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(57) Abstract

Group B streptococcus (GBS) proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.

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GROUP B STREPTOCOCCUS ANTIGENS

FIELD OF THE INVENTION

The present invention is related to antigens, more particularly protein antigens of group B streptococcus (GBS) bacterial pathogen which are useful as vaccine components for therapy and/or prophylaxis.

BACKGROUND OF THE INVENTION

Streptococcus are gram (+) bacteria that are differentiated by group specific carbohydrate antigens A through O found on their cell surface. Streptococcus groups are further distinguished by type-specific capsular polysaccharide antigens. Several serotypes have been identified for the Group B streptococcus (GBS) : Ia, Ib, II, III, IV, V, VI, VII and VIII. GBS also contains antigenic proteins known as "C-proteins" (alpha, beta, gamma and delta), some of which have been cloned.

Although GBS is a common component of the normal human vaginal and colonic flora this pathogen has long been recognized as a major cause of neonatal sepsis and meningitis, late-onset meningitis in infants, postpartum endometritis as well as mastitis in dairy herds. Expectant mothers exposed to GBS are at risk of postpartum infection and may transfer the infection to their baby as the child passes through the birth canal. Although the organism is sensitive to antibiotics, the high attack rate and rapid onset of sepsis in neonates and meningitis in infants results in high morbidity and mortality.

To find a vaccine that will protect individuals from GBS infection, researches have turned to the type-specific antigens. Unfortunately these polysaccharides have proven to be poorly immunogenic in humans and are restricted to the particular serotype from which the polysaccharide originates. Further, capsular polysaccharide elicit a T cell independent response i.e. no IgG production. Consequently capsular polysaccharide antigens are unsuitable as a vaccine component for protection against GBS infection.

Others have focused on the C-protein beta antigen which demonstrated immunogenic properties in mice and rabbit models. This protein was found to be unsuitable as a human vaccine because of its undesirable property of interacting with high affinity and in a non-immunogenic manner with the Fc region of human IgA. The C-protein alpha antigen is rare in type III serotypes of GBS which is the serotype responsible for most GBS mediated conditions and is therefore of little use as a vaccine component.

Therefore there remains an unmet need for GBS antigens that may be used as vaccine components for the prophylaxis and/or therapy of GBS infection.

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,

SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

In other aspects, there is provided vectors comprising polynucleotides of the invention operably linked to an expression control region, as well as host cells transfected with said vectors and methods of producing polypeptides comprising culturing said host cells under conditions suitable for expression.

In yet another aspect, there is provided novel polypeptides encoded by polynucleotides of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a is the DNA sequence of clone 1 (SEQ ID NO :1) with corresponding amino acid sequences for open reading frames;
figure 1b is the amino acid sequence SEQ ID NO: 2;
figure 1c is the amino acid sequence SEQ ID NO: 3;
figure 1d is the amino acid sequence SEQ ID NO: 4;
figure 1e is the amino acid sequence SEQ ID NO: 5;
figure 1f is the amino acid sequence SEQ ID NO: 6;

Figure 2a is the DNA sequence of clone 2 (SEQ ID NO :7) with corresponding amino acid sequences for open reading frames;
figure 2b is the amino acid sequence SEQ ID NO: 8;
figure 2c is the amino acid sequence SEQ ID NO: 9;
figure 2d is the amino acid sequence SEQ ID NO:10;
figure 2e is the amino acid sequence SEQ ID NO:11;
figure 2f is the amino acid sequence SEQ ID NO:12;

Figure 3a is the DNA sequence of clone 3 (SEQ ID NO :13) with corresponding amino acid sequences for open reading frames;
figure 3b is the amino acid sequence SEQ ID NO:14;
figure 3c is the amino acid sequence SEQ ID NO:15;
figure 3d is the amino acid sequence SEQ ID NO:16;
figure 3e is the amino acid sequence SEQ ID NO:17;
figure 3f is the amino acid sequence SEQ ID NO:18;
figure 3g is the amino acid sequence SEQ ID NO:19;
figure 3h is the amino acid sequence SEQ ID NO:20;
figure 3i is the amino acid sequence SEQ ID NO:21;

Figure 4a is the DNA sequence of clone 4 (SEQ ID NO :22) with corresponding amino acid sequences for open reading frames;
figure 4b is the amino acid sequence SEQ ID NO:23;
figure 4c is the amino acid sequence SEQ ID NO:24;
figure 4d is the amino acid sequence SEQ ID NO:25;
figure 4e is the amino acid sequence SEQ ID NO:26;

Figure 5a is the DNA sequence of clone 5 (SEQ ID NO :27) with corresponding amino acid sequences for open reading frames;
figure 5b is the amino acid sequence SEQ ID NO:28;
figure 5c is the amino acid sequence SEQ ID NO:29;
figure 5d is the amino acid sequence SEQ ID NO:30;
figure 5e is the amino acid sequence SEQ ID NO:31;

Figure 6a is the DNA sequence of clone 6 (SEQ ID NO :32) ;
figure 6b is the amino acid sequence SEQ ID NO:33;
figure 6c is the amino acid sequence SEQ ID NO:34;
figure 6d is the amino acid sequence SEQ ID NO:35;
figure 6e is the amino acid sequence SEQ ID NO:36;

Figure 7a is the DNA sequence of clone 7 (SEQ ID NO :37);
figure 7b is the amino acid sequence SEQ ID NO:38;

figure 7c is the amino acid sequence SEQ ID NO:39;
figure 7d is the amino acid sequence SEQ ID NO:40;
figure 7e is the amino acid sequence SEQ ID NO:41;

Figure 8 is the DNA sequence of a part of clone 7 including a signal sequence (SEQ ID NO :42);

Figure 9 is the DNA sequence of a part of clone 7 without a signal sequence (SEQ ID NO :43);
Figure 9a is the amino acid sequence (SEQ ID NO:44);

Figure 10 represents the distribution of anti-GBS ELISA titers in sera from CD-1 mice immunized with recombinant GBS protein corresponding to the SEQ ID NO:39.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel antigenic polypeptides of group B streptococcus (GBS) characterized by the amino acid sequence selected from the group consisting of:

SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

A preferred embodiment of the invention includes SEQ ID NO :39 and SEQ ID NO:44.

A further preferred embodiment of the invention is SEQ ID NO :39.

A further preferred embodiment of the invention is SEQ ID NO :44.

As used herein, "fragments", "derivatives" or "analogs" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural.

The terms «fragments», «derivatives» or «analogues» of polypeptides of the present invention also include polypeptides which are modified by addition, deletion,

substitution of amino acids provided that the polypeptides retain the capacity to induce an immune response.

By the term «conserved amino acid» is meant a substitution of one or more amino acids for another in which the antigenic determinant (including its secondary structure and hydropathic nature) of a given antigen is completely or partially conserved in spite of the substitution.

For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity, which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

Preferably, derivatives and analogs of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70% of the residues are the same. More preferably polypeptides will have greater than 95% homology. In another preferred embodiment, derivatives and analogs of polypeptides of the invention will have fewer than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.

Furthermore, in those situations where amino acid regions are found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively mimic the different epitopes of the different GBS strains.

Also included are polypeptides which have fused thereto other compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro- sequences; and (poly)saccharides.

Moreover, the polypeptides of the present invention can be modified by terminal $-NH_2$ acylation (eg. by acetylation, or thioglycolic acid amidation, terminal carbosy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers such as avidin/biotin, gluteraldehyde or dimethyl-superimidate. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology.
Preferably, a fragment, analog or derivative of a polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers (i.e. synthetic multimers), polypeptides may be utilized having bishaloacetyl groups, nitroarylhalides, or the like,

where the reagents being specific for thio groups. Therefore, the link between two mercapto groups of the different peptides may be a single bond or may be composed of a linking group of at least two, typically at least four, and not more than 16, but usually not more than about 14 carbon atoms.

In a particular embodiment, polypeptide fragments, analogs and derivatives of the invention do not contain a methionine (Met) starting residue. Preferably, polypeptides will not incorporate a leader or secretory sequence (signal sequence). The signal portion of a polypeptide of the invention may be determined according to established molecular biological techniques. In general, the polypeptide of interest may be isolated from a GBS culture and subsequently sequenced to determine the initial residue of the mature protein and therefor the sequence of the mature polypeptide.

According to another aspect, there is provided vaccine compositions comprising one or more GBS polypeptides of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant.

Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e. $AlK(SO_4)_2$, $AlNa(SO_4)_2$, $AlNH_4(SO_4)_2$, $Al(OH)_3$, $AlPO_4$, silica, kaolin; saponin derivative; carbon polynucleotides i.e. poly IC and poly AU and also detoxified cholera toxin (CTB)and E.coli heat labile toxin for induction of mucosal immunity. Preferred adjuvants include QuilA™, Alhydrogel™ and Adjuphos™. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral.

Vaccine compositions of the invention are used for the treatment or prophylaxis of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus* infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. General information about Streptococcus is available in Manual of Clinical Microbiology by P.R.Murray et al.(1995, 6th Edition, ASM Press, Washington, D.C.). More particularly group B *streptococcus*, *agalactiae*. In a particular embodiment vaccines are administered to those individuals at risk of GBS infection such as pregnant women and infants for sepsis, meningitis and pneumonia as well as immunocompromised individuals such as those with diabetes, liver disease or cancer. Vaccines may also have veterinary applications such as for the treatment of mastitis in cattle which is mediated by the above mentioned bacteria as well as *E.coli*.

The vaccine of the present invention can also be used for the manufacture of a medicament used for the treatment or prophylaxis of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus* infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. More particularly group B *streptococcus*, *agalactiae*.

Vaccine compositions are preferably in unit dosage form of about 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 12 weeks intervals between immunizations, and more preferably 1 to 6

weeks.

According to another aspect, there is provided polynucleotides encoding polypeptides of group B streptococcus (GBS) characterized by the amino acid sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

Preferred polynucleotides are those illustrated in figures 1a (SEQ ID NO: 1), 2a (SEQ ID NO: 7), 3a (SEQ ID NO: 13), 4a (SEQ ID NO: 22), 5a (SEQ ID NO: 27), 6a (SEQ ID NO: 32), 7a (SEQ ID NO: 37), 8 (SEQ ID NO : 42) and 9(SEQ ID NO : 43) which correspond to the open reading frames, encoding polypeptides of the invention.

Preferred polynucleotides are those illustrated in figures 1a (SEQ ID NO: 1), 2a (SEQ ID NO: 7), 3a (SEQ ID NO: 13), 4a (SEQ ID NO: 22), 5a (SEQ ID NO: 27), 6a (SEQ ID NO: 32), 7a (SEQ ID NO: 37), 8 (SEQ ID NO : 42) and 9(SEQ ID NO : 43) and fragments, analogues and derivatives thereof.

More preferred polynucleotides of the invention are those illustrated in Figures 7 (SEQ ID NO : 37), 8 (SEQ ID NO : 42) and 9(SEQ ID NO : 43).

Most preferred polynucleotides of the invention are those illustrated in Figures 8 (SEQ ID NO : 42) and 9(SEQ ID NO :

43).

It will be appreciated that the polynucleotide sequences illustrated in the figures may be altered with degenerate codons yet still encode the polypeptides of the invention.

Due to the degeneracy of nucleotide coding sequences, other polynucleotide sequences which encode for substantially the same polypeptides of the present invention may be used in the practice of the present invention. These include but are not limited to nucleotide sequences which are altered by the substitution of different codons that encode the same amino acid residue within the sequence, thus producing a silent change.

Accordingly the present invention further provides polynucleotides which hybridize to the polynucleotide sequences herein above described (or the complement sequences thereof) having 50% and preferably at least 70% identity between sequences. More preferably polynucleotides are hybridizable under stringent conditions i.e. having at least 95% identity and most preferably more than 97% identity.

By capable of hybridizing under stringent conditions is meant annealing of a nucleic acid molecule to at least a region of a second nucleic acid sequence (whether as cDNA, mRNA, or genomic DNA) or to its complementary strand under standard conditions, e.g. high temperature and/or low salt content, which tend to disfavor hybridization of noncomplementary nucleotide sequences. A suitable protocol is described in Maniatis T. et al., Molecular cloning : A Laboratory Manual, Cold Springs Harbor Laboratory, 1982, which is herein incorporated by reference.

In a further aspect, polynucleotides encoding polypeptides

of the invention, or fragments, analogs or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is replicable and expressible upon injection thereby producing the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional in eukaryotic cells. Preferably the vector is injected intramuscularly.

According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of oligopeptides which are ligated to produce the full polypeptide (block ligation).

For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes. Suitable vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide sequence may be incorporated in the vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control element). One can select individual components of the expression control region that are appropriate for a given

host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor, N.Y., 1989 incorporated herein by reference). Suitable promoters include but are not limited to LTR or SV40 promoter, *E.coli* lac, tac or trp promoters and the phage lambda P_L promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicillin resistance gene. Suitable bacterial vectors include pET, pQE70, pQE60, pQE-9, pbs, pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. *E.coli*, *Bacillus subtilis*, *Streptomyces*; fungal i.e. *Aspergillus niger*, *Aspergillus nidulins*; yeast i.e. *Saccharomyces* or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are typically harvested by centrifugation then disrupted by physical or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate may be achieved by established techniques depending on the properties of the polypeptide i.e. using ammonium sulfate or ethanol precipitation , acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography. Final purification may be achieved using HPLC.

The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be removed using post-translational processing (see US

4,431,739; 4,425,437; and 4,338,397 incorporated herein by reference) or be chemically removed subsequent to purifying the expressed polypeptide.

According to a further aspect, the GBS polypeptides of the invention may be used in a diagnostic test for streptococcus infection in particular GBS infection. Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may be followed:

a) obtaining a biological sample from a patient;
b) incubating an antibody or fragment thereof reactive with a GBS polypeptide of the invention with the biological sample to form a mixture; and
c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of streptococcus.

Alternatively, a method for the detection of antibody specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:

a) isolating a biological sample from a patient;
b) incubating one or more GBS polypeptides of the invention or fragments thereof with the biological sample to form a mixture; and
c) detecting specifically bound antigen or bound fragment in the mixture which indicates the presence of antibody specific to streptococcus.

One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially to determine whether antibodies specific for the protein are present in an organism.

The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:

a) isolating the biological sample from a patient;
b) incubating one or more DNA probes having a DNA sequence encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and
c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. GBS nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labeled with a detectable label. A preferred DNA probe for this application is an oligomer having a sequence complementary to at least about 6 contiguous nucleotides of the GBS polypeptides of the invention.

Another diagnostic method for the detection of streptococcus in a patient comprises:

a) labeling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;
b) administering the labeled antibody or labeled fragment to the patient; and
c) detecting specifically bound labeled antibody or labeled fragment in the patient which indicates the presence of streptococcus.

A further aspect of the invention is the use of the GBS

polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in particular the treatment of streptococcus infection. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may in general belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which were produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the GBS polypeptides but is preferably specific for one.

EXAMPLE 1 Murine model of lethal Group B Streptococcus (GBS) infection

The mouse model of GBS infection is described in detail in Lancefield et al (J Exp Med 142:165-179,1975). GBS strain C388/90 (Clinical isolate obtained in 1990 from the cephalorachidian fluid of a patient suffering from meningitis, Children's Hospital of Eastern Ontario, Ottawa, Canada) and NCS246 (National Center for Streptococcus, Provincial Laboratory of Public Health for Northern Alberta, Edmonton, Canada) were respectively serotyped as type Ia/c and type II/R.

To increase their virulence, the GBS strains C388/90 (serotype Ia/c) and NCS 246 (serotype II/R) were serially passaged through mice as described previously (Lancefield et al. J Exp Med 142:165-179, 1975). Briefly, the increase of virulence was monitored using intraperitoneal inoculations of serial dilutions of a subculture in Todd-Hewitt broth obtained from either the blood or spleen of infected mice. After the last passage, infected blood samples were used to inoculate Todd-Hewitt broth. After an incubation of 2 hours at 37°C with 7% CO_2, glycerol at a final concentration of 10% (v/v) was added to the culture. The culture was then aliquoted and stored at -80° C for use in GBS challenge experiments. The number of cfu of GBS present in these frozen samples was determined. The bacterial concentration necessary to kill 100% (LD100) of the 18 weeks old mice were determined to be $3.5X10^5$ and $1.1X10^5$ respectively for GBS strain C388/90 and NCS246, which corresponded to a significant increase in virulence for both strains. Indeed, the LD100 recorded before the passages for these two strains was higher than 10^9 cfu.

In a bacterial challenge, a freshly thawed aliquot of a virulent GBS strain was adjusted to the appropriate bacterial concentration using Todd-Hewitt broth and 1ml was injected intraperitoneally to each female CD-1 mouse. The mice used for the passive protection experiments were 6 to 8 weeks old, while the ones used for the active protection experiments were approximately 18 weeks old at the time of the challenge. All inocula were verified by colony counts. Animals were observed for any sign of infection four times daily for the first 48 h after challenge and then daily for the next 12 days. At the end of that period, blood samples were obtained from the survivors and frozen at -20°C. The spleen obtained from each mouse that survived the challenge was cultured in order to identify any remaining GBS.

EXAMPLE 2 Immunization and protection in mice with formaldehyde killed whole GBS cells

Formaldehyde killed GBS whole cells were prepared according to the procedures described in Lancefield et al (J Exp Med 142:165-179,1975). Briefly, an overnight culture on sheep blood agar plates (Quelab Laboratories, Montreal, Canada) of a GBS strain was washed twice in PBS buffer (phosphate buffered-saline, pH7.2), adjusted to approximately $3X10^9$ cfu/mL and incubated overnight in PBS containing 0.3% (v/v) formaldehyde. The killed GBS suspension was washed with PBS and kept frozen at -80°C.

Female CD-1 mice, 6 to 8 weeks old (Charles River, St-Constant, Québec, Canada), were injected subcutaneously three times at two weeks interval with 0.1 ml of formaldehyde killed cells of GBS strain C388/90 (~$6X10^7$ GBS), or 0.1 ml of PBS for the control group. On the day before the immunization, Alhydrogel™ (Superfos Biosector, Frederikssund, Denmark) at a final concentration of 0.14 mg or 0.21 mg of Al, was added to these preparations and incubated overnight at 4°C with agitation. Serum samples were obtained from each mouse before the beginning of the immunization protocol and two weeks after the last injection. The sera were frozen at -20°C.

Eight mice in each control group injected with PBS and the group immunized with formaldehyde killed whole cells GBS strain C388/90 (Ia/c) were challenged with $1.5X10^4$ cfu of GBS strain C388/90 (Ia/c) one week after the third injection. All mice immunized with the formaldehyde killed GBS whole cells survived the homologous challenge while, within 5 days after the challenge, only 4 out of the 8 mice injected with PBS survived from the infection. In order to increase the mortality rate in the control groups, the

bacterial suspension had to be adjusted according to the age of the mice at the time of the bacterial challenge. In subsequent challenge experiments, when mice were older than 15 weeks, the bacterial inoculum was increased to concentrations between $3.0X10^5$ and $2.5X10^6$ cfu.

Table 1 Immunization of CD1 mice with formaldehyde killed whole cells of GBS and subsequent homologous challenge [strain C388/90 (Ia/c)] and heterologous challenge [strain NCS246 (II/R)].

antigenic preparations used for immunization[1]	number of living mice 14 days after the bacterial challenge (% Survival)	
	homologous challenge: strain C388/90 (Ia/c)	heterologous challenge: strain NCS246 (II/R)
1st infection		
formaldehyde killed cells of GBS strain C388/90 (Ia/c)[2]	8/8 (100)[3]	n.d.[5]
control PBS	4/8 (50)	n.d.
2nd infection		
formaldehyde killed cells of GBS strain C388/90 (Ia/c)	6/6 (100)[4]	0/6 (0)[6]
control PBS	2/6 (33)	0/6 (0)

[1] alhydrogel™ at a final concentration of 0.14 mg or 0.21mg of Al was used;
[2] approximately $6X10^7$ cfu;
[3] intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to $1.5X10^4$ cfu;
[4] intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to $2.1X10^6$ cfu;
[5] not done;
[6] intraperitoneal challenge with 1 mL Todd-Hewitt culture medium containing GBS NCS246 (II/R) suspension adjusted to $1.2X10^5$ cfu.

In another experiment, one group of 12 mice corresponding to a control group was injected with PBS, while a second group of 12 mice was immunized with formaldehyde killed whole cells of GBS strain C388/90 (Ia/c). Six mice from each of these two groups were challenged with $2.1X10^6$ cfu of the GBS strain C388/90 (Ia/c) (Table I). As the first challenge experiment, all mice immunized with the GBS strain C388/90 (Ia/c) survived the homologous challenge. Only two out of the 6 mice injected with PBS survived the infection.

The remaining 6 mice in both groups were then used one week later to verify whether this antigenic preparation could confer cross protection against strain NCS246 (II/R) which produce a serologically distinct capsule. None of the mice infected with this second GBS strain survived the infection. The later result suggested that most of the protective immune response induced by formaldehyde killed strain C388/90 is directed against the capsular polysaccharide and that it could be restricted to strains of that particular serotype. These results clearly indicated that this particular model of infection can be efficiently used to study the protection conferred by vaccination.

EXAMPLE 3 Immunization of rabbit with formaldehyde killed whole GBS cells and passive protection in mice

A New Zealand rabbit (2.5 kg, Charles River, St-Constant, Québec, Canada) was immunized with formaldehyde killed cells of GBS strain C388/90 (Ia/c) to obtain hyperimmune serum. This rabbit was injected subcutaneously three times at three weeks interval with approximately $1.5X10^9$ cfu of formaldehyde killed whole cells of GBS strain C388/90 (Ia/c). Freund's complete adjuvant (Gibco BRL Life Technologies, Grand Island, New York) was used as the adjuvant for the first immunization, while Freund's incomplete adjuvant (Gibco BRL) was used for the following two injections. Serum samples were obtained before the beginning of the immunization protocol and two weeks after the last injection. The sera were frozen at -20°C.

The ability of this particular rabbit hyperimmune serum to passively protect mice against a lethal infection with GBS

was also evaluated. Intraperitoneal injection of mice with either 15 or 25 µL of hyperimmune rabbit serum 18 hours before the challenge protected 4 out of 5 mice (80%) against the infection. Comparatively, survival rates lower than 20% were recorded for mice in the control group injected with PBS or serum obtained from a rabbit immunized with meningococcal outer membrane preparation. This result clearly indicates that the immunization of another animal species with killed GBS cells can induce the production of antibodies that can passively protect mice. This reagent will also be used to characterize clones.

Table 2 Passive protection of CD-1 mice conferred by rabbit serum obtained after immunization with formaldehyde killed group B whole streptococci (strain C388/90 (Ia/c)) antigenic preparation

groups	number of living mice 14 days after the bacterial challenge with GBS strain C388/90 (Ia/c)[2]	% survival
rabbit hyperimmune serum[2] - 25 µl	4/5	80
rabbit hyperimmune serum[1] - 15 µl	4/5	80
control rabbit serum - 25 µl	1/5	20
control PBS	1/10	10

[1] Freund's complete adjuvant was used for first immunization, and Freund's incomplete adjuvant for the following two injections;
[2] intraperitoneal challenge with 1 ml Todd-Hewitt culture medium containing GBS C388/90 (Ia/c) suspension adjusted to $2X10^4$ cfu.

EXAMPLE 4 Recombinant production of His.Tag-GBS fusion protein

The coding region of a GBS gene was amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from the genomic DNA of GBS strain C388/90 (Ia/c) using the oligos that contained base extensions for the addition of the restriction sites BglII (AGATCT) and HindIII (AAGCTT), respectively. The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglII and HindIII (Pharmacia Canada Inc Baie d'Urfe, Canada), and extracted with phenol:chloroform before ethanol precipitation. The pET-32b(+) vector (Novagen, Madison, WI) containing the thioredoxin-His.Tag sequence was digested with the restriction enzymes BglII and HindIII, extracted with phenol:chloroform, and then ethanol precipitated. The BglII-HindIII genomic DNA fragment was ligated to the BglII-HindIII pET-32b(+) vector to create the coding sequence for thioredoxin-His.Tag-GBS fusion protein whose gene was under control of the T7 promoter. The ligated products were transformed into *E. coli* strain XLI Blue MRF'(Δ(*mcr*A)183Δ (*mcr*CB-*hsd*SMR-*mrr*)173 *end*A1 *sup*E44 *thi*-1 *rec*A1 *gyr*A96 *rel*A1 lac [F'*pro*AB *lac*I^{q}ZΔM15Tn10 (Tet^{r})]^{c}) (Stratagene, La Jolla, CA) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed.), pp. 109-135). The recombinant pET plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The recombinant pET plasmid was transformed by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) into *E. coli* strain AD494 (DE3) (Δ*ara*$^{-}$*leu*7697 Δ*lac*X74 Δ*pho*A *Pvu*II *pho*R Δ*mal*F3 F'[*lac*$^{+}$(*lac*I^{q}) *pro*] *trx*B::Kan (DE3)) (Novagen, Madison, WI). In this strain of

E. coli, the T7 promoter controlling expression of the fusion protein, is specifically recognized by the T7 RNA polymerase (present on the λDE3 prophage) whose gene is under the control of the lac promoter which is inducible by isopropyl-β-D-thio-galactopyranoside (IPTG).

The transformant AD494(DE3)/rpET was grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, Yeast extract 5g/L, NaCl 10g/L) containing 100μg of ampicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per mL until the A_{600} reached a value of 0.6. In order to induce the production of the thioredoxin-His.Tag-GBS fusion protein, the cells were incubated for 2 additional hours in the presence of IPTG at a final concentration of 1mM. The bacterial cells were harvested by centrifugation.

The recombinant fusion protein produced by AD494(DE3)/rpET32 upon IPTG induction for 2h was partially obtained as insoluble inclusion bodies which were purified from endogenous *E. coli* proteins by the isolation of insoluble aggregates (Gerlach, G.F. et al 1992, Infect. Immun. 60:892). Induced cells from a 500 mL culture were resuspended in 20 mL of 25% sucrose-50mM Tris-HCl buffer (pH8.0) and frozen at -70°C. Lysis of cells in thawed suspension was achieved by the addition of 5mL of a solution of lysozyme (10mg/mL) in 250mM Tris-HCl buffer (pH8.0) followed by an incubation of 10 to 15 min on ice, and the addition of 150mL of detergent mix (5 parts of 20mM Tris-HCl buffer [pH7.4]-300mM NaCl-2% deoxycholic acid-2% Nonidet P-40 and 4 parts of 100mM Tris-HCl buffer [pH8]-50mM EDTA-2% Triton X-100) followed by 5 min incubation on ice. Upon sonication, protein aggregates were harvested by centrifugation for 30 min at 35,000 X g and a sample of the soluble cellular fraction was kept. The aggregated proteins were solubilized in 6M guanidine hydrochloride. The

presence of the fusion protein in both the soluble and insoluble fractions was shown by Western Blot analysis using the serum of a mouse injected with formaldehyde killed cells of GBS strain C388/90 (Ia/c) that survived a bacterial challenge with the corresponding GBS strain.

The purification of the fusion protein from the soluble fraction of IPTG-induced AD494(DE3)/rpET was done by affinity chromatography based on the properties of the His.Tag sequence (6 consecutive histidine residues) to bind to divalent cations (Ni^{2+}) immobilized on the His.Bind metal chelation resin (Novagen, Madison, WI). The purification method used are those described in the pET system Manual, 6th Edition (Novagen, Madison, WI). Briefly, the pelleted cells obtained from a 100mL culture induced with IPTG was resuspended in 4mL of Binding buffer (5mM imidazole-500mM NaCl-20mM Tris-HCl pH7.9), sonicated, and spun at 39,000 X g for 20 min to remove debris. The supernatant was filtered (0.45µm pore size membrane) and deposited on a column of His.Bind resin equilibrated in Binding buffer. The column was then washed with 10 column volumes of Binding buffer followed by 6 column volumes of Wash buffer (20mM imidazole-500mM NaCl-20mM Tris-HCl pH7.9). The thioredoxin-His.Tag-GBS fusion protein was eluted with Elute buffer (1M imidazole-500mM NaCl-20mM Tris-HCl pH7.9). The removal of the salt and imidazole from the sample was done by dialysis against 3 X 1 liter PBS at 4°C.

The quantities of fusion protein obtained from either the soluble or insoluble cytoplasmic fractions of *E. coli* were estimated by Coomassie staining of a sodium dodecyl sulfate (SDS)-polyacrylamide gel with serial dilutions of these proteins and a bovine serum albumin standard (Pierce Chemical Co. Rockford, Ill.).

EXAMPLE 5 Recombinant production of GBS protein under control of lambda P_L promoter

The DNA coding region of a GBS protein was inserted downstream of the promoter λP_L into the translation vector pURV22. This plasmid was derived from p629 (George et al, 1987, Bio/Technology 5:600) from which the coding region for a portion of the herpes simplex virus type I (HSV-I) glycoprotein (gD-1) was removed and the ampicillin resistance gene replaced by a kanamycin cassette obtained from the plasmid vector pUC4K (Pharmacia Biotech Canada Inc., Baie D'Urfe, Canada). The vector contained a cassette of the bacteriophage λ cI857 temperature sensitive repressor gene from which the functional P_R promoter had been deleted. The inactivation of the cI857 repressor by temperature increase from the ranges of 30-37°C to 37-42°C resulted in the induction of the gene under the control of λ P_L. The translation of the gene was controlled by the ribosome binding site cro followed downstream by a BglII restriction site (AGATCT) and the ATG: ACTAAGGAGGTTAGATCTATG.

Restriction enzymes and T4 DNA ligase were used according to suppliers (Pharmacia Biotech Canada Inc., Baie D'Urfe, Canada; and New England Biolabs Ltd., Mississauga, Canada). Agarose gel electrophoresis of DNA fragments was performed as described by Sambrook et al. (Molecular cloning : A laboratory Manual, 1989, Cold Spring Harbor Laboratory Press, N.Y). Chromosomal DNA of the GBS bacteria was prepared according to procedures described in Jayarao et al (J. Clin. Microbiol., 1991, 29:2774). DNA amplification reactions by polymerase chain reaction (PCR) were made using DNA Thermal Cycler GeneAmp PCR system 2400 (Perkin Elmer, San Jose, CA). Plasmids used for DNA sequencing were purified using plasmid kits from Qiagen (Chatsworth, CA). DNA fragments were purified from agarose gels using Qiaex II

gel extraction kits from Qiagen (Chatsworth, CA). Plasmid transformations were carried out by the method described by Hanahan (DNA Cloning, Glover (ed.) pp, 109-135, 1985). The sequencing of genomic DNA inserts in plasmids was done using synthetic oligonucleotides which were synthesized by oligonucleotide synthesizer model 394 (the Perkin-Elmer Corp., Applied Biosystems Div. (ABI), Foster City, CA). The sequencing reactions were carried out by PCR using the Taq Dye Deoxy Terminator Cycle Sequencing kit (ABI, Foster City, CA) and DNA electrophoresis was performed on automated DNA sequencer 373A (ABI, Foster City, CA). The assembly of the DNA sequence was performed using the program Sequencer 3.0 (Gene Codes Corporation, Ann Arbor, MI). Analysis of the DNA sequences and their predicted polypeptides was performed with the program Gene Works version 2.45 (Intelligenetics, Inc., Mountain View CA).

The coding region of the GBS gene was amplified by PCR from GBS strain C388/90 (Ia/c) genomic DNA using oligos that contained base extensions for the addition of restriction sites BglII (AGATCT) and XbaI(TCTAGA), respectively. The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglII and XbaI, and extracted with phenol:chloroform before ethanol precipitation. The pURV22 vector was digested with the restriction enzymes BglII and XbaI, extracted with phenol:chloroform, and ethanol precipitated. The BglII-XbaI genomic DNA fragment was ligated to the BglII-XbaI pURV22 vector in which the GBS gene was under the control of the λPL promoter. The ligated products were transformed into *E. coli* strain XLI Blue MRF' (Δ (*mcr*A)183Δ(*mcr*CB-*hsd*SMR-mrr)173 *end*A1 *sup*E44 *thi*-1 recA1 *gyr*A96 *rel*A1 lac[F' *pro*AB *lac*I^{q}ZΔM15 Tn10(Tet^{r})]^{c}) (Stratagene, La Jolla CA) according to the methods described in Hanahan, supra. Transformants harboring plasmids with the

insert were identified by analysis of lysed cells submitted to electrophoresis on agarose gel (Sambrook et al, supra). The recombinant pURV22 plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

The transformant XLI Blue MRF'/rpURV22 was grown at 34°C with agitation at 250 rpm in LB broth containing 50µg of kanamycin per mL until the A_{600} reached a value of 0.6. In order to induce the production of the fusion protein, the cells were incubated for 4 additional hours at 39°C. The bacterial cells were harvested by centrifugation , resuspended in sample buffer, boiled for 10 min and kept at -20°C.

EXAMPLE 6 Subcloning GBS protein gene in CMV plasmid pCMV-GH

The DNA coding region of a GBS protein was inserted in phase downstream of the human growth hormone (hGH) gene which was under the transcriptional control of the cytomegalovirus (CMV) promoter in the plasmid vector pCMV-GH (Tang et al, Nature, 1992, 356:152). The CMV promoter is non functional in E. coli cells but active upon administration of the plasmid in eukaryotic cells. The vector also incorporated the ampicillin resistance gene.

The coding region of the gene was amplified by PCR from genomic DNA of GBS strain C388/90 (Ia/c) using the oligos that contained base extensions for the addition of the restriction sites BglII (AGATCT) and HindIII (AAGCTT). The PCR product was purified from agarose gel using a Qiaex II gel extraction kit from Qiagen (Chatsworth, CA), digested with the restriction enzymes BglII and HindIII, and extracted with phenol:chloroform before ethanol precipitation. The pCMV-GH vector (Laboratory of Dr. Stephen

A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas) containing the human growth hormone to create fusion proteins was digested with the restriction enzymes BamHI and HindIII, extracted with phenol:chloroform, and ethanol precipitated. The 1.3-kb BglII-HindIII genomic DNA fragment was ligated to the BamHI -HindIII pCMV-GH vector to create the hGH-GBS fusion protein under the control of the CMV promoter. The ligated products were transformed into *E. coli* strain DH5α[φ80 *lac*Z ΔM15 *end*A1 *rec*A1 *hsd*R17 ($^{r}K^{-m}K^{+}$) *sup*E44 *thi*-1λ^{-} *gyr*A96 *rel*A1 Δ(*lac*ZYA-*arg*F)U169] (Gibco BRL, Gaithersburg, MD) according to the methods described by Hanahan, supra. Transformants harboring plasmids with the insert were identified by analysis of lysed cells submitted to electrophoresis on agarose gel (Sambrook, J. et al , supra). The recombinant pCMV plasmid was purified using a Qiagen kit (Qiagen, Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

EXAMPLE 7 Immunological activity of GBS protein to GBS challenge

Four groups of 12 female CD-1 mice (Charles River, St-Constant, Quebec, Canada) of 6 to 8 weeks were injected subcutaneously three times at three week intervals with 0.1mL of the following antigenic preparations: formaldehyde killed cells of GBS strain C388/90 (~$6X10^{7}$ cfu), 20μg of thioredoxin-His.Tag-GBS fusion protein obtained from the insoluble (inclusion bodies) or 20μg of the fusion protein, affinity purified (nickel column), from the soluble cytoplasmic fraction in *E.coli*, or 20μg of affinity purified (nickel column) thioredoxin-His.Tag control polypeptide. 20μg of QuilA™ (Cedarlane Laboratories Ltd, Hornby, Canada)

was added to each antigenic preparation as the adjuvant. Serum samples were obtained from each mouse before immunization (PB) and on days 20 (TB1), 41 (TB2) and 54 (TB3) during the immunization protocols. Sera were frozen at -20°C.

An increase of the ELISA titers was recorded after each injection of the fusion protein indicating a good primary response and a boost of the specific humoral immune response after each of the second and third administration. At the end of the immunization period, the means of reciprocal ELISA titers was 456,145 for the group immunized with 20μg of fusion protein obtained from inclusion bodies compared to 290,133 for the group of mice immunized with the protein from soluble fraction in *E.coli*. The latter result suggests that the protein obtained from inclusion bodies could be more immunogenic than the soluble protein. Analysis of mice sera in ELISA using the affinity purified thioredoxin-His.Tag to coat plates showed that negligible antibody titers are made against the thioredoxin-His.Tag portion of the fusion protein. The reactivity of the sera from mice injected with the recombinant fusion protein was also tested by ELISA against formaldehyde killed whole cells of GBS strain C388/90. The antibodies induced by immunization with recombinant fusion protein also recognized their specific epitopes on GBS cells indicating that their conformation is close enough to the native streptococcal protein to induce cross-reactive antibodies.

To verify whether the immune response induced by immunization could protect against GBS infection, mice were challenged with $3.5X10^5$ cfu of GBS strains C338/90(Ia/c) and $1.2X10^5$ cfu of strain NCS246(II/R) the results of which are illustrated in tables 3 and 4 respectively. Mice immunized with control thioredoxin-His.Tag peptide were not protected against challenge with either GBS strain while those

immunized with formaldehyde killed C388/90 whole cells only provided protection against homologous challenge. The thioredoxin-His.Tag-GBS fusion protein of the invention protected mice from challenge with both GBS strains. Blood and spleen culture of these mice did not reveal the presence of any GBS.

Table 3 Survival from GBS strain C388/90 (Ia/c) challenge[1]

immunizing agent	no. mice surviving challenge	% survival
thioredoxin-His.Tag[2]	1 / 6	17
formaldehyde killed C388/90 cells[3]	6 / 6	100
thioredoxin-His.Tag-GBS fusion (inclusion body preparation)[4]	6 / 6	100
thioredoxin-His.Tag-GBS fusion (cytoplasmic fraction)[4]	6 / 6	100

[1] intraperitoneal administration with 1 ml Todd-Hewitt culture medium adjusted to $3.5X10^5$ cfu;
[2] 20μg administered; posterior legs paralyzed in surviving mouse; GBS detected in blood and spleen;
[3] $6X10^7$ cfu administered;
[4] 20μg administered.

Table 4 Survival from GBS strain NCS246 (II/R) challenge[1]

immunizing agent	no. mice surviving challenge	% survival
thioredoxin-His.Tag[2]	0 / 6	0
formaldehyde killed C388/90 cells[3]	2 / 6	34
thioredoxin-His.Tag-GBS fusion (inclusion body preparation)[2]	5 / 5[4]	100
thioredoxin-His.Tag-GBS fusion (cytoplasmic fraction)[2]	6 / 6	100

[1] intraperitoneal administration with 1 ml Todd-Hewitt culture medium containing GBS NCS246(II/R) suspension adjusted to $1.2X10^5$ cfu.
[2] 20µg administered;
[3] $6X10^7$ cfu administered;
[4] one mouse died during immunization.

EXAMPLE 8 Immunization with recombinant GBS protein confers protection against experimental GBS infection

This example illustrates the protection of mice against fatal GBS infection by immunization with the recombinant protein corresponding to the SEQ ID NO:39.

Groups of 10 female CD-1 mice (Charles River) were immunized subcutaneously three times at three-week intervals with 20 µg of recombinant protein purified from E. coli strain BLR (Novagen) harboring the recombinant pURV22 plasmid vector containing the GBS gene corresponding to SEQ ID NO:42 in presence of 20 µg of QuilA™ adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada) or, as control, with

QuilA™ adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and fourteen days (day 57) following the third injection. One week later the mice were challenged with approximately 10^4 to 10^6 CFU of various virulent GBS strains. Samples of the GBS challenge inoculum were plated on TSA/5% sheep blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 14 days and on day 14 post-challenge, the surviving mice were sacrificed and blood and spleen were tested for the presence of GBS organisms. The survival data are shown in table 5.

Prechallenge sera were analyzed for the presence of antibodies reactive with GBS by standard immunoassays. Elisa and immunoblot analyses indicated that immunization with recombinant GBS protein produced in *E. coli* elicited antibodies reactive with both, recombinant and native GBS protein. Antibody responses to GBS are described in Example 9.

Table 5. Ability of recombinant GBS protein corresponding to SEQ ID NO: 39 to elicit protection against 8 diverse GBS challenge strains

	Challenge strain			
Immunogen	Designation	Type	No. alive:	No. dead [1]
rGBS protein none	C388/90	Ia/c	8 : 2 0 : 10	(P<0.0001)
rGBS protein none	NCS 246	II/R	10 : 0 3 : 7	(P=0.0012)
rGBS protein none	ATCC12401	Ib	10 : 0 3 : 7	(P=0.001)
rGBS protein none	NCS 535	V	10 : 0 5 : 5	(P=0.01)
rGBS protein none	NCS 9842	VI	10 : 0 0 : 10	(P<0.0001)
rGBS protein NCS 915-F[3] none	NCS 915	III	7 : 3 1 : 9 4 : 6	(P=0.0007)[2]
rGBS protein NCS 954-F none	NCS 954	III/R	7 : 3 4 : 6 1 : 9	(P=0.002)
rGBS protein COH1-F none	COH1	III	4 : 6 3 : 7 0 : 10	(P=0.0004)

[1] Groups of 10 mice per group were used, the number of mice surviving to infection and the number of dead mice are indicated. The survival curves corresponding to recombinant GBS protein-immunized animals were compared to the survival curves corresponding to mock-immunized animals using the log-rank test for nonparametric analysis.

[2] Comparison analysis to NCS915-F-immunized animals.

[3] Animals were immunized with formaldehyde-killed GBS in presence of QuilA™ adjuvant.

All hemocultures from surviving mice were negative at day 14 post-challenge. Spleen cultures from surviving mice were negative except for few mice from experiment MB-11.

EXAMPLE 9 Vaccination with the recombinant GBS protein elicits an immune response to GBS

Groups of 10 female CD-1 mice were immunized subcutaneously with recombinant GBS protein corresponding to SEQ ID NO:39 as described in Example 8. In order to assess the antibody response to native GBS protein, sera from blood samples collected prior each immunization and fourteen days after the third immunization were tested for antibody reactive with GBS cells by ELISA using plates coated with formaldehyde-killed GBS cells from type III strain NCS 954, type Ib strain ATCC12401, type V strain NCS 535 or type VI strain NCS 9842. The specificity of the raised antibodies for GBS protein was confirmed by Western blot analyses to GBS cell extracts and purified recombinant antigens. The results shown in Figure 10 clearly demonstrate that animals respond strongly to recombinant GBS protein used as immunogens with median reciprocal antibody titers varying between 12000 and 128000, for sera collected after the third immunization, depending of the coating antigen. All preimmune sera were negative when tested at a dilution of 1 :100. GBS-reactive antibodies were detectable in the sera of each animal after a single injection of recombinant GBS protein.

Example 10 Antigenic conservation of the GBS protein of the present invention

Monoclonal antibodies (MAbs) specific to the GBS protein of the present invention were used to demonstrate that this surface antigen is produced by all GBS and that it is also antigenically highly conserved.

A collection of 68 GBS isolates was used to evaluate the reactivity of the GBS-specific MAbs. These strains were obtained from the National Center for Streptococcus, Provincial Laboratory of Public Health for Northern Alberta, Canada; Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, Quebec, Canada; American Type Culture Collection, USA; Laboratoire de Sante Publique du Quebec, Canada; and Dept. of Infectious Disease, Children's Hospital and Medical Center, Seattle, USA. All eight Mabs were tested against the following panel of strains: 6 isolates of serotype Ia or Ia/c, 3 isolates of serotype Ib, 4 isolates of serotype II, 14 isolates of serotype III, 2 isolates of serotype IV, 2 isolates of serotype V, 2 isolates of serotype VI, 2 isolates of serotype VII, 1 isolate of serotype VIII, 10 isolates that were not serotyped and 3 bovine *S. agalactiae* strains. MAb 3A2 was also reacted with additional GBS: 9 isolates of serotype Ia/c and 10 isolates of serotype V. The strains were grown overnight on blood agar plates at 37°C in an atmosphere of 5% CO_2. Cultures were stored at -70°C in heart infusion broth with 20% (v/v) glycerol.

To obtain the GBS protein-specific MAbs, mice were immunized three times at three-week intervals with 20 μg of purified recombinant GBS protein (SEQ ID NO :44) in the presence of 20% QuilA™ adjuvant. Hybridoma cell lines were generated by fusion of spleen cells recovered from immunized mice with the nonsecreting SP2/O myeloma cell line as described

previously (Hamel, J. et al. 1987. J. Med. Microbiol. 23:163-170). Hybrid clone supernatants were tested for specific antibody production by ELISA using formaldehyde inactivated GBS and purified recombinant GBS protein (SEQ ID NO :39 or 44) as coating antigen, as previously described (Hamel, J. et al. 1987. J. Med. Microbiol. 23:163-170). Specific hybrid were cloned by limiting dilutions, expanded, and frozen in liquid nitrogen. Production of recombinant GBS protein was presented in Examples 4 & 5. Purified recombinant GBS protein or formaldehyde inactivated GBS were resolved by electrophoresis by using the discontinuous buffer system of Laemmli as recommended by the manufacturer and then transfer onto nitrocellulose membrane for Western immunoblotting as described previously (Martin et al. 1992. Infect. Immun. 60:2718-2725).

Western immunoblotting experiments clearly indicated that all eight MAbs recognized a protein band that corresponded to the purified recombinant GBS protein (SEQ ID NO :39). These MAbs also reacted with a protein band present in every GBS isolates tested so far. The reactivity of these GBS-specific MAbs are presented in Table 6. Each MAb reacted well with all 46 GBS. In addition, these MAbs also recognized the 3 *S. agalactiae* strains of bovine origin that were tested. MAb 3A2 also recognized nineteen GBS; 9 isolates of serotype Ia/c and 10 of serotype V. The other MAbs were not tested against these additional strains.

These results demonstrated that the GBS protein (SEQ ID NO :39) was produced by all the 65 GBS and the three 3 *S. agalactiae* strains of bovine origin that were tested so far. More importantly, these results clearly demonstrated that the epitopes recognized by these eight GBS-specific MAbs were widely distributed and conserved among GBS. These results also indicated that these epitopes were not

restricted to serologically related isolates since representatives of all known GBS serotypes including the major disease causing groups were tested.

In conclusion, the data presented in this example clearly demonstrated that the GBS protein of the present invention is produced by all GBS and that it is antigenically highly conserved.

Table 6. Reactivity of eight GBS protein-specific MAbs with different *S. agalactiae* strains as evaluated by Western immunoblots.

Mabs	Number of each serotype of *s. agalactiae* strains recognized by the MAbs.										
	Ia or Ia/c (6)	Ib (3)	II (4)	III (4)	IV (2)	V (2)	VI (2)	VII (2)	VIII (1)	NT(10)[2]	TOTAL (26)	Bovine (3)
3A2[1]	6	3	4	4	2	2	2	2	1	10	46	3
5A12	6	3	4	4	2	2	2	2	1	10	46	3
6G11	6	3	4	4	2	2	2	2	1	10	46	2
8B9	6	3	4	4	2	2	2	2	1	10	46	3
8E11	6	3	4	4	2	2	2	2	1	10	46	3
12B12	6	3	4	4	2	2	2	2	1	10	46	3
18F11	6	3	4	4	2	2	2	2	1	10	46	3
20G2	6	3	4	4	2	2	2	2	1	10	46	3

1 Nine additional strains of serotype Ia/c and 10 strains of serotype V were recognized by MAb 3A2.
2 These strains were not serotyped

WE CLAIM:

1. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence selected from the group consisting of:
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

2. A polynucleotide according to claim 1, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.

3. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence selected from the group consisting of:
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

4. An isolated polynucleotide that is complementary to the polynucleotide of claim 1.

5. An isolated polynucleotide that is complementary to the polynucleotide of claim 3.

6. The polynucleotide of claim 1, wherein said polynucleotide is DNA.

7. The polynucleotide of claim 3, wherein said polynucleotide is DNA.

8. The polynucleotide of claim 1, wherein said polynucleotide is RNA.

9. The polynucleotide of claim 3, wherein said polynucleotide is RNA.

10. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence selected from the group consisting of : SEQ ID NO : 1, SEQ ID NO : 7, SEQ ID NO : 13, SEQ ID NO : 22, SEQ ID NO : 27, SEQ ID NO : 32, SEQ ID NO : 37, SEQ ID NO : 42 and SEQ ID NO : 43 or fragments, analogues or derivatives thereof.

11. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence selected from the group consisting of : SEQ ID NO : 37, SEQ ID NO : 42 and SEQ ID NO : 43.

12. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 37.

13. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 42.

14. A polynucleotide according to claim 11 which hybridizes under stringent conditions to a second polynucleotide having the sequence SEQ ID NO : 43.

15. A polynucleotide according to claim 10 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.

16. A polynucleotide according to claim 11 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.

17. A vector comprising the polynucleotide of claim 1, wherein said polynucleotide is operably linked to an expression control region.

18. A vector comprising the polynucleotide of claim 3, wherein said polynucleotide is operably linked to an expression control region.

19. A host cell transfected with the vector of claim 17.

20. A host cell transfected with the vector of claim 18.

21. A process for producing a polypeptide comprising culturing a host cell according to claim 19 under conditions suitable for expression of said polypeptide.

22. A process for producing a polypeptide comprising culturing a host cell according to claim 20 under condition suitable for expression of said polypeptide.

23. An isolated polypeptide having at least 70% identity to a second polypeptide having a sequence selected from the group consisting of:
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

24. The isolated polypeptide of claim 23 having a sequence according to SEQ ID NO : 39.

25. The isolated polypeptide of claim 23 having a sequence according to SEQ ID NO : 44.

26. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence selected from the group consisting of:
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:44 or fragments, analogs or derivatives thereof.

27. The isolated polypeptide of claim 26 having a sequence according to SEQ ID NO : 39.

28. The isolated polypeptide of claim 26 having a sequence according to SEQ ID NO : 44.

29. An isolated polypeptide having an amino acid sequence selected from the group consisting of:
SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40 and SEQ ID NO:41 or fragments, analogs or derivatives thereof.

30. The isolated polypeptide of claim 29 having an amino acid sequence according to SEQ ID NO : 39.

31. An isolated polypeptide having an amino acid sequence according to SEQ ID NO : 44.

32. An isolated polypeptide according to any one of claims 29 to 31, wherein the N-terminal Met residue is deleted.

33. An isolated polypeptide according to any one of claims 29 to 30, wherein the secretory amino acid sequence is deleted.

34. A vaccine composition comprising a polypeptide according to any one of claims 23 to 31 and a pharmaceutically acceptable carrier, diluent or adjuvant.

35. A vaccine composition comprising a polypeptide according to claim 32 and a pharmaceutically acceptable carrier, diluent or adjuvant.

36. A vaccine composition comprising a polypeptide according to claim 33 and a pharmaceutically acceptable carrier, diluent or adjuvant.

37. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 34.

38. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 35.

39. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of a composition according to claim 36.

40. A method according to any one of claims 37 to 39, wherein said animal is a bovine.

41. A method according to any one of claims 37 to 39, wherein said animal is a human.

42. A method according to any one of claims 37 to 39, wherein said bacterial infection is selected from the group consisting of group A streptococcus and group B streptococcus.

43. A method according to claim 42, wherein said bacterial infection is group B streptococcus.

44. Use of a vaccine composition according to claim 34 for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

45. Use of a vaccine composition according to any one of claims 35 to 36 for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

46. Use of a vaccine composition according to any one claims 23 to 31 for the manufacture of a vaccine for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

47. Use of a vaccine composition according to claim 32 for the manufacture of a vaccine for the therapeutic or

prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

48. Use of a vaccine composition according to claim 33 for the manufacture of a vaccine for the therapeutic or prophylactic treatment of streptococcal bacterial infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the composition.

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TATCTGGCAA AGAGCCAGCT AATCGTTTTA GTTGGGCTAA AAATAAATTA TTAATCAATG     60
  S  G  K   E  P  A   N  R  F  S   W  A  K   N  K  L   L  I  N  G
 ---->
GATTCATTGC AACTCTAGCA GCAACTATCT TATTTTTTGC AGTTCAATTC ATAGGTCTTA    120
  F  I  A   T  L  A   A  T  I  L   F  F  A   V  Q  F   I  G  L  K

AACCAGATTA CCCTGGAAAA ACCTACTTTA TTATCCTATT GACAGCATGG ACTTTGATGG    180
  P  D  Y   P  G  K   T  Y  F  I   I  L  L   T  A  W   T  L  M  A

CATTAGTAAC TGCTTTAGTG GGATGGGATA ATAGGTATGG TTCCTTCTTG TCGTTATTAA    240
  L  V  T   A  L  V   G  W  D  N   R  Y  G   S  F  L   S  L  L  I

TATTATTATT CCAGCTTGGT TCAAGCGCAG GAACTTACCC AATAGAATTG AGTCCTAAGT    300
  L  L  F   Q  L  G   S  S  A  G   T  Y  P   I  E  L   S  P  K  F

TCTTTCAAAC AATTCAACCA TTTTTACCGA TGACTTACTC TGTTTCAGGA TTAAGAGAGA    360
  F  Q  T   I  Q  P   F  L  P  M   T  Y  S   V  S  G   L  R  E  T

CCATCTCGTT GACGGGAGAC GTTAACCATC AATGGAGAAT GCTAGTAATC TTTTTAGTAT    420
  I  S  L   T  G  D   V  N  H  Q   W  R  M   L  V  I   F  L  V  S

CATCGATGAT ACTTGCTCTT CTTATTTATC GTAAACAAGA AGATTAATAG AAAGTATCTA    480
  S  M  I   L  A  L   L  I  Y  R   K  Q  E   D

GTGATAGACT AACAGTATGA TATGGTATGT CAAAGTATTT AGGAGGAGAA GATATGTCTA    540
                                                          M  S  T
                                                         |---->
CTTTAACAAT AATTATTGCA ACATTAACTG CTTTGGAACA TTTTTATATT ATGTATTTGG    600
  L  T  I   I  I  A   T  L  T  A   L  E  H   F  Y  I   M  Y  L  E

AGACGTTAGC CACCCAGTCA AATATGACTG GGAAGATTTT TAGTATGTCT AAAGAAGAGT    660
  T  L  A   T  Q  S   N  M  T  G   K  I  F   S  M  S   K  E  E  L

TGTCATATTT ACCCGTTATT AAACTTTTTA AGAATCAAGG TGTATACAAC GGCTTGATTG    720
  S  Y  L   P  V  I   K  L  F  K   N  Q  G   V  Y  N   G  L  I  G

GCCTATTCCT CCTTTATGGG TTATATATTT CACAGAATCA AGAAATTGTA GCTGTTTTTT    780
  L  F  L   L  Y  G   L  Y  I  S   Q  N  Q   E  I  V   A  V  F  L

TAATCAATGT ATTGCTAGTT GCTATTTATG GTGCTTTGAC AGTTGATAAA AAAATCTTAT    840
  I  N  V   L  L  V   A  I  Y  G   A  L  T   V  D  K   K  I  L  L

TAAAACAGGG TGGTTTACCT ATATTAGCTC TTTTAACATT CTTATTTTAA TACTACTTAG    900
  K  Q  G   G  L  P   I  L  A  L   L  T  F   L  F

CCGTTCGATT TAGTTGAACG GCTTTTAGTA ATCATTTTTT TCTCATAATA CAGGTAGTTT    960

AAGTAATTTG TCTTTAAAAA TAGTATAATA TAACTACGAA TTCAAAGAGA GGTGACTTTG   1020

ATTATGACTG AGAACTGGTT ACATACTAAA GATGGTTCAG ATATTTATTA TCGTGTCGTT   1080
    M  T  E   N  W  L   H  T  K   D  G  S  D   I  Y  Y   R  V  V
   |---->
GGTCAAGGTC AACCGATTGT TTTTTTACAT GGCAATAGCT TAAGTAGTCG CTATTTTGAT   1140
 G  Q  G  Q   P  I  V   F  L  H   G  N  S  L   S  S  R   Y  F  D

AAGCAAATAG CATATTTTTC TAAGTATTAC CAAGTTATTG TTATGGATAG TAGAGGGCAT   1200
 K  Q  I  A   Y  F  S   K  Y  Y   Q  V  I  V   M  D  S   R  G  H

GGCAAAAGTC ATGCAAAGCT AAATACCATT AGTTTCAGGC AAATAGCAGT TGACTTAAAG   1260
 G  K  S  H   A  K  L   N  T  I   S  F  R  Q   I  A  V   D  L  K
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GATATCTTAG TTCATTTAGA GATTGATAAA GTTATATTGG TAGGCCATAG CGATGGTGCC   1320
D  I  L  V   H  L  E   I  D  K   V  I  L  V   G  H  S   D  G  A

AATTTAGCTT TAGTTTTTCA AACGATGTTT CCAGGTATGG TTAGAGGGCT TTTGCTTAAT   1380
N  L  A  L   V  F  Q   T  M  F   P  G  M  V   R  G  L   L  L  N

TCAGGGAACC TGACTATTCA TGGTCAGCGA TGGTGGGATA TTCTTTTAGT AAGGATTGCC   1440
S  G  N  L   T  I  H   G  Q  R   W  W  D  I   L  L  V   R  I  A

TATAAATTCC TTCACTATTT AGGGAAACTC TTTCCGTATA TGAGGCAAAA AGCTCAAGTT   1500
Y  K  F  L   H  Y  L   G  K  L   F  P  Y  M   R  Q  K   A  Q  V

ATTTCGCTTA TGTTGGAGGA TTTGAAGATT AGTCCAGCTG ATTTACAGCA TGTGTCAACT   1560
I  S  L  M   L  E  D   L  K  I   S  P  A  D   L  Q  H   V  S  T

CCTGTAATGG TTTTGGTTGG AAATAAGGAC ATAATTAAGT TAAATCATTC TAAGAAACTT   1620
P  V  M  V   L  V  G   N  K  D   I  I  K  L   N  H  S   K  K  L

GCTTCTTATT TTCCAAGGGG GGAGTTTTAT TCTTTAGTTG GCTTTGGGCA TCACATTATT   1680
A  S  Y  F   P  R  G   E  F  Y   S  L  V  G   F  G  H   H  I  I

AAGCAAGATT CCCATGTTTT TAATATTATT GCAAAAAAGT TTATCAACGA TACGTTGAAA   1740
K  Q  D  S   H  V  F   N  I  I   A  K  K  F   I  N  D   T  L  K

GGAGAAATTG TTGAAAAAGC TAATTGAAAA AGTCAAATCA CTGACTTCTG TGATTAAAAT   1800
G  E  I  V   E  K  A   N

TGTATTTTTT ATATCTGTTT TAGTGCTTAT TATTGTTGAA ATGATTCATT TGAAACGAAC   1860
                                            M  I  H  L   K  R  T
                                            |---->

TATTTCTGTT GAGCAACTAA AGAGTGTTTT TGGGCAATTA TCTCCAATGA ATCTTTTCTT   1920
I  S  V   E  Q  L  K   S  V  F   G  Q  L   S  P  M  N   L  F  L

AATTATCCTT GTGGGGGTTA TCGCTGTCTT ACCGACAACC GGATATGACT TTGTACTGAA   1980
I  I  L   V  G  V  I   A  V  L   P  T  T   G  Y  D  F   V  L  N

TGGACTTTTA CGTACAGATA AAAGCAAAAG GTATATTTTA CAGACTAGTT GGTGTATCAA   2040
G  L  L  R   T  D  K  S   K  R  Y   I  L  Q   T  S  W   C  I  N

CACTTTTAAT AACTTGTCAG GATTCGGTGG CTTAATCGAT ATTGGGTTGC GCATGGCTTT   2100
T  F  N  N   L  S  G   F  G  G   L  I  D  I   G  L  R   M  A  F

TTATGGTAAA AAAGGTCAAG AGAAGAGTGA CCTAAGAGAA GTGACTCGTT TTTTACCCTA   2160
Y  G  K  K   G  Q  E   K  S  D   L  R  E  V   T  R  F   L  P  Y

TCTTATTTCT GGTCTGTCAT TTATTAGTGT GATTGCCTTA ATCATGAGCC ATATTTTTCA   2220
L  I  S  G   L  S  F   I  S  V   I  A  L  I   M  S  H   I  F  H

TGCCAAAGCT AGTGTTGATT ACTATTATTT GGTATTAATT GGTGCTAGTA TGTATTTTCC   2280
A  K  A  S   V  D  Y   Y  Y  L   V  L  I  G   A  S  M   Y  F  P

TGTTATTTAT TGGATTTCTG GTCATAAAGG AAGCCATTAT TTCGGAGATA TGCCATCTAG   2340
V  I  Y  W   I  S  G   H  K  G   S  H  Y  F   G  D  M   P  S  S

TACTCGTATA AAATTAGGTG TTGTTTCTTT TTTTGAATGG GGATGTGCGG CCGCAGCATT   2400
T  R  I  K   L  G  V   V  S  F   F  E  W  G   C  A  A   A  A  F

TATAATTATC GGTTATTTAA TGGGCATTCA TCTACCAGTT TATAAAATTT TACCACTATT   2460
I  I  I  G   Y  L  M   G  I  H   L  P  V  Y   K  I  L   P  L  F
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TTGTATTGGT TGTGCCGTCG GGATTGTATC CCTTATTCCC GGTGGATTAG GAAGTTTTGA 2520
C I G C A V G I V S L I P G G L G S F E

ATTAGTTCTA TTTACAGGGT TTGCTGCCGA GGGACTACCT AAAGAAACTG TGGTTGCATG 2580
L V L F T G F A A E G L P K E T V V A W

GTTATTACTT TATCGTTTAG CCTACTATAT TATTCCATTC TTTGCAGGTA TCTATTTCTT 2640
L L L Y R L A Y Y I I P F F A G I Y F F

TATCCATTAT TTAGGTAGTC AAATAAATCA ACGTTATGAA AATGTCCCGA AAGAGTTAGT 2700
I H Y L G S Q I N Q R Y E N V P K E L V

ATCAACTGTT CTACAAACCA TGGTGAGCCA TTTGATGCGT ATTTTAGGTG CATTCTTAAT 2760
S T V L Q T M V S H L M R I L G A F L I
|---->

ATTTTCAACA GCATTTTTTG AAAATATTAC TTATATTATG TGGTTGCAGA AGCTAGGCTT 2820
F S T A F F E N I T Y I M W L Q K L G L

GGACCCATTA CAAGAACAAA TGTTATGGCA GTTTCCAGGT TTATTGCTGG GGGTTTGTTT 2880
D P L Q E Q M L W Q F P G L L L G V C F

TATTCTCTTA GCTAGAACTA TTGATCAAAA AGTGAAAAAT GCTTTTCCAA TTGCTATTAT 2940
I L L A R T I D Q K V K N A F P I A I I

CTGGATTACT TTGACATTGT TTTATCTTAA TTTAGGTCAT ATTAGTTGGC GACTATCTTT 3000
W I T L T L F Y L N L G H I S W R L S F

CTGGTTTATT TTACTATTGT TAGGCTTATT AGTCATTAAG CCAACTCTCT ATAAAAAACA 3060
W F I L L L L G L L V I K P T L Y K K Q

ATTTATTTAT AGCTGGGAAG AGCGTATTAA GGATGGAATC ATTATCGTTA GTTTAATGGG 3120
F I Y S W E E R I K D G I I I V S L M G

AGTTCTATTT TATATTGCAG GACTACTATT CCCTATCAGG GCTCATATTA CAGGTGGTAG 3180
V L F Y I A G L L F P I R A H I T G G S

TATTGAACGC CTGCATTATA TCATAGCATG GGAGCCGATA GCATTGGCTA CGTTGATTCT 3240
I E R L H Y I I A W E P I A L A T L I L

TACTCTCGTT TATTTATGTT TGGTTAAGAT TTTACAAGGA AAATCTTGTC AGATTGGTGA 3300
T L V Y L C L V K I L Q G K S C Q I G D

TGTGTTCAAT GTGGATCGTT ATAAAAAACT ACTTCAAGCT TACGGTGGTT CTTCGGATAG 3360
V F N V D R Y K K L L Q A Y G G S S D S

CGGTTTAGCC TTTTTAAATG ATAAAAGGCT CTACTGGTAC CAAAAAAATG GAGAAGATTG 3420
G L A F L N D K R L Y W Y Q K N G E D C

CGTTGCGTTC CAATTTGTAA TTGTCAATAA TAAATGTCTT ATTATGGGGG AACCAGCCGG 3480
V A F Q F V I V N N K C L I M G E P A G

TGATGACACT TATATTCGTG AAGCTATTGA ATCGTTTATT GATGATGCTG ATAAGCTAGA 3540
D D T Y I R E A I E S F I D D A D K L D

CTATGACCTT GTTTTTTACA GTATTGGACA GAAGTTGACA CTACTTTTAC ATGAGTATGG 3600
Y D L V F Y S I G Q K L T L L L H E Y G

TTTTGACTTT ATGAAAGTTG GTGAGGATGC TTTAGTTAAT TTAGAAACGT TTACTCTTAA 3660
F D F M K V G E D A L V N L E T F T L K

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AGGGAATAAG TACAAACCTT TCAGAAATGC CCTAAATAGA GTTGAAAAGG ATGGTTTCTA   3720
 G  N  K  Y  K  P  F  R  N  A  L  N  R  V  E  K  D  G  F  Y

TTTCGAAGTT GTACAATCGC CACATAGTCA AGAGCTACTA AATAGTTTGG AAGAGATTTC   3780
 F  E  V  V  Q  S  P  H  S  Q  E  L  L  N  S  L  E  E  I  S

TAATACTTGG TTAGAAGGAC GTCCTGAAAA AGGTTTCTCA CTAGGATATT TTAATAAAGA   3840
 N  T  W  L  E  G  R  P  E  K  G  F  S  L  G  Y  F  N  K  D

TTATTTCCAA CAAGCCCCAA TAGCTTTGGT AAAAAATGCT GAACACGAAG TTGTTGCTTT   3900
 Y  F  Q  Q  A  P  I  A  L  V  K  N  A  E  H  E  V  V  A  F

TGCTAATATT ATGCCAAACT ATGAAAAGAG TATTATCTCT ATTGATTTAA TGCGTCACGA   3960
 A  N  I  M  P  N  Y  E  K  S  I  I  S  I  D  L  M  R  H  D

TAAACAGAAA ATTCCGAATG GCGTTATGGA TTTCCTCTTT TTATCATTAT TCTCTTATTA   4020
 K  Q  K  I  P  N  G  V  M  D  F  L  F  L  S  L  F  S  Y  Y

TCAAGAGAAG GGATACCACT ATTTTGATTT GGGGATGGCA CCTTTATCAG GAGTTGGTCG   4080
 Q  E  K  G  Y  H  Y  F  D  L  G  M  A  P  L  S  G  V  G  R

CGTTGAAACA AGTTTGCTA AAGAGAGAAT GGCGTATCTT GTCTATCATT TCGGTAGTCA   4140
 V  E  T  S  F  A  K  E  R  M  A  Y  L  V  Y  H  F  G  S  H

TTTCTACTCA TTTAATGGTT TACACAAGTA TAAGAAGAAG TTTACACCAT TGTGGTCGGA   4200
 F  Y  S  F  N  G  L  H  K  Y  K  K  K  F  T  P  L  W  S  E

ACGTTATATT TCTTGTTCTC GTTCGTCCTG GTTAATTTGT GCTATTTGTG CCCTATTAAT   4260
 R  Y  I  S  C  S  R  S  S  W  L  I  C  A  I  C  A  L  L  M

GGAAGATAGT AAAATTAAGA TTGTTAAATA AGCTTTATTT GGCAATTAAA AAGAGCATGT   4320
 E  D  S  K  I  K  I  V  K

CATGCGACAT GCTCTTTTTA AATCATTTAA TACCATTGAT TGCTTGAATC TACTTTATAA   4380

TATGATGTGC TTTTAAATAT TGTTTAGCTA CTGTAGCTGC TGATTTATGC TTTACAGCTA   4440

CTTGGTAGTT CATTTCTTGC ATTTCTTTTT CAGTGATATG ACCAGCAAGT TTATTGAGAG   4500

CTTTTTTTAC TTGA  (SEQ ID NO:1)                                      4514
```

FIG. 1a
[clone1-dna/aa]

SGKEPANRFS WAKNKLLING FIATLAATIL FFAVQFIGLK PDYPGKTYFI 50
ILLTAWTLMA LVTALVGWDN RYGSFLSLLI LLFQLGSSAG TYPIELSPKF 100
FQTIQPFLPM TYSVSGLRET ISLTGDVNHQ WRMLVIFLVS SMILALLIYR 150
KQED (SEQ ID NO:2) 154

FIG. 1b

MSTLTIIIAT LTALEHFYIM YLETLATQSN MTGKIFSMSK EELSYLPVIK 50
LFKNQGVYNG LIGLFLLYGL YISQNQEIVA VFLINVLLVA IYGALTVDKK 100
ILLKQGGLPI LALLTFLF (SEQ ID NO:3) 118

FIG. 1c

MTENWLHTKD GSDIYYRVVG QGQPIVFLHG NSLSSRYFDK QIAYFSKYYQ 50
VIVMDSRGHG KSHAKLNTIS FRQIAVDLKD ILVHLEIDKV ILVGHSDGAN 100
LALVFQTMFP GMVRGLLLNS GNLTIHGQRW WDILLVRIAY KFLHYLGKLF 150
PYMRQKAQVI SLMLEDLKIS PADLQHVSTP VMVLVGNKDI IKLNHSKKLA 200
SYFPRGEFYS LVGFGHHIIK QDSHVFNIIA KKFINDTLKG EIVEKAN 247
(SEQ ID NO:4)

FIG. 1d

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MIHLKRTISV EQLKSVFGQL SPMNLFLIIL VGVIAVLPTT GYDFVLNGLL   50
RTDKSKRYIL QTSWCINTFN NLSGFGGLID IGLRMAFYGK KGQEKSDLRE  100
VTRFLPYLIS GLSFISVIAL IMSHIFHAKA SVDYYYLVLI GASMYFPVIY  150
WISGHKGSHY FGDMPSSTRI KLGVVSFFEW GCAAAAFIII GYLMGIHLPV  200
YKILPLFCIG CAVGIVSLIP GGLGSFELVL FTGFAAEGLP KETVVAWLLL  250
YRLAYYIIPF FAGIYFFIHY LGSQINQRYE NVPKELVSTV LQTMVSHLMR  300
ILGAFLIFST AFFENITYIM WLQKLGLDPL QEQMLWQFPG LLLGVCFILL  350
ARTIDQKVKN AFPIAIIWIT LTLFYLNLGH ISWRLSFWFI LLLLGLLVIK  400
PTLYKKQFIY SWEERIKDGI IIVSLMGVLF YIAGLLFPIR AHITGGSIER  450
LHYIIAWEPI ALATLILTLV YLCLVKILQG KSCQIGDVFN VDRYKKLLQA  500
YGGSSDSGLA FLNDKRLYWY QKNGEDCVAF QFVIVNNKCL IMGEPAGDDT  550
YIREAIESFI DDADKLDYDL VFYSIGQKLT LLLHEYGFDF MKVGEDALVN  600
LETFTLKGNK YKPFRNALNR VEKDGFYFEV VQSPHSQELL NSLEEISNTW  650
LEGRPEKGFS LGYFNKDYFQ QAPIALVKNA EHEVVAFANI MPNYEKSIIS  700
IDLMRHDKQK IPNGVMDFLF LSLFSYYQEK GYHYFDLGMA PLSGVGRVET  750
SFAKERMAYL VYHFGSHFYS FNGLHKYKKK FTPLWSERYI SCSRSSWLIC  800
AICALLMEDS KIKIVK   (SEQ ID NO:5)                       816
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FIG. 1e

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MRILGAFLIF STAFFENITY IMWLQKLGLD PLQEQMLWQF PGLLLGVCFI   50
LLARTIDQKV KNAFPIAIIW ITLTLFYLNL GHISWRLSFW FILLLLGLLV  100
IKPTLYKKQF IYSWEERIKD GIIIVSLMGV LFYIAGLLFP IRAHITGGSI  150
ERLHYIIAWE PIALATLILT LVYLCLVKIL QGKSCQIGDV FNVDRYKKLL  200
QAYGGSSDSG LAFLNDKRLY WYQKNGEDCV AFQFVIVNNK CLIMGEPAGD  250
DTYIREAIES FIDDADKLDY DLVFYSIGQK LTLLLHEYGF DFMKVGEDAL  300
VNLETFTLKG NKYKPFRNAL NRVEKDGFYF EVVQSPHSQE LLNSLEEISN  350
TWLEGRPEKG FSLGYFNKDY FQQAPIALVK NAEHEVVAFA NIMPNYEKSI  400
ISIDLMRHDK QKIPNGVMDF LFLSLFSYYQ EKGYHYFDLG MAPLSGVGRV  450
ETSFAKERMA YLVYHFGSHF YSFNGLHKYK KKFTPLWSER YISCSRSSWL  500
ICAICALLME DSKIKIVK   (SEQ ID NO:6)                     518
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FIG. 1f

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AATTTTGATA TCGAAACAAC AACTTTTGAG GCAATGAAAA AGCACGCGTC ATTATTGGAG    60
N  F  D  I   E  T  T   T  F  E   A  M  K  K   H  A  S   L  L  E
---->
AAAATATCTG TTGAGCGTTC TTTTATTGAA TTTGATAAAC TTCTATTAGC ACCTTATTGG   120
K  I  S  V   E  R  S   F  I  E   F  D  K  L   L  L  A   P  Y  W
CGTAAAGGAA TGCTGGCACT AATAGATAGT CATGCTTTTA ATTATCTACC ATGCTTAAAA   180
R  K  G  M   L  A  L   I  D  S   H  A  F  N   Y  L  P   C  L  K
AATAGGGAAT TACAATTAAG CGCCTTTTTG TCCCAGTTAG ATAAAGATTT TTTATTTGAG   240
N  R  E  L   Q  L  S   A  F  L   S  Q  L  D   K  D  F   L  F  E
ACATCAGAAC AAGCTTGGGC ATCACTCATC TTGAGTATGG AAGTTGAACA CACAAAGACT   300
T  S  E  Q   A  W  A   S  L  I   L  S  M  E   V  E  H   T  K  T
TTTTTAAAAA AATGGAAGAC ATCAACTCAC TTTCAAAAAG ATGTTGAGCA TATAGTGGAT   360
F  L  K  K   W  K  T   S  T  H   F  Q  K  D   V  E  H   I  V  D
GTTTATCGTA TTCGTGAACA AATGGGATTG GCTAAAGAAC ATCTTTATCG TTATGGAAAA   420
V  Y  R  I   R  E  Q   M  G  L   A  K  E  H   L  Y  R   Y  G  K
ACTATAATAA AACAAGCGGA AGGTATTCGC AAAGCAAGAG GCTTGATGGT TGATTTCGAA   480
T  I  I  K   Q  A  E   G  I  R   K  A  R  G   L  M  V   D  F  E
AAAATAGAAC AACTAGATAG TGAGTTAGCA ATCCATGATA GGCATGAGAT AGTTGTCAAT   540
K  I  E  Q   L  D  S   E  L  A   I  H  D  R   H  E  I   V  V  N
GGTGGCACCT TAATCAAGAA ATTAGGAATA AAACCTGGTC CACAGATGGG AGATATTATC   600
G  G  T  L   I  K  K   L  G  I   K  P  G  P   Q  M  G   D  I  I
TCTCAAATTG AATTAGCCAT TGTTTTAGGA CAACTGATTA ATGAAGAAGA GGCTATTTTA   660
S  Q  I  E   L  A  I   V  L  G   Q  L  I  N   E  E  E   A  I  L
CATTTTGTTA AGCAGTACTT GATGGATTAG AGAGGATTAT ATGAGCGATT TTTTAGTAGA   720
H  F  V  K   Q  Y  L   M  D                  M  S  D  F   L  V  D
                                             |----->
TGGATTGACT AAGTCGGTTG GTGATAAGAC GGTCTTTAGT AATGTTTCAT TTATCATCCA   780
 G  L  T   K  S  V  G   D  K  T   V  F  S   N  V  S  F   I  I  H
TAGTTTAGAC CGTATTGGGA TTATTGGTGT CAATGGAACT GGAAAGACAA CACTATTAGA   840
 S  L  D   R  I  G  I   I  G  V   N  G  T   G  K  T  T   L  L  D
TGTTATTTCG GGTGAATTAG GTTTTGATGG TGATCGTTCC CCTTTTTCAT CAGCTAATGA   900
 V  I  S   G  E  L  G   F  D  G   D  R  S   P  F  S  S   A  N  D
TTATAAGATT GCTTATTTAA AACAAGAACC AGACTTTGAT GATTCTCAGA CAATTTTGGA   960
 Y  K  I   A  Y  L  K   Q  E  P   D  F  D   D  S  Q  T   I  L  D
CACCGTACTT TCTTCTGACT TAAGAGAGAT GGCTTTAATT AAAGAATATG AATTATTGCT  1020
 T  V  L   S  S  D  L   R  E  M   A  L  I   K  E  Y  E   L  L  L
TAATCACTAC GAAGAAAGTA AGCAATCACG TCTAGAGAAA GTAATGGCAG AAATGGATTC  1080
 N  H  Y   E  E  S  K   Q  S  R   L  E  K   V  M  A  E   M  D  S
TTTAGATGCT TGGTCTATTG AGAGCGAAGT CAAAACAGTA TTATCCAAAT TAGGTATTAC  1140
 L  D  A   W  S  I  E   S  E  V   K  T  V   L  S  K  L   G  I  T
TGATTTGCAG TTGTCGGTTG GTGAATTATC AGGAGGATTA CGAAGACGTG TTCAATTAGC  1200
 D  L  Q   L  S  V  G   E  L  S   G  G  L   R  R  R  V   Q  L  A
```

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GCAAGTATTA TTAAATGATG CAGATTTATT GCTCTTAGAC GAACCTACTA ACCACTTAGA  1260
 Q  V  L   L  N  D  A   D  L  L   L  L  D   E  P  T  N   H  L  D

TATTGACACT ATTGCATGGT TAACGAATTT TTTGAAAAAT AGTAAAAAGA CAGTGCTTTT  1320
 I  D  T   I  A  W  L   T  N  F   L  K  N   S  K  K  T   V  L  F

TATAACTCAT GATCGTTATT TTCTAGACAA TGTTGCAACA CGTATTTTTG AATTAGATAA  1380
 I  T  H   D  R  Y  F   L  D  N   V  A  T   R  I  F  E   L  D  K

GGCACAGATT ACAGAATATC AAGGCAATTA TCAGGATTAT GTCCGACTTC GTGCAGAACA  1440
 A  Q  I   T  E  Y  Q   G  N  Y   Q  D  Y   V  R  L  R   A  E  Q

AGACGAGCGT GATGCTGCTA GTTTACATAA AAAGAAACAG CTTTATAAAC AGGAACTAGC  1500
 D  E  R   D  A  A  S   L  H  K   K  K  Q   L  Y  K  Q   E  L  A

TTGGATGCGT ACTCAGCCAC AAGCTCGTGC AACGAAACAA CAGGCTCGTA TTAATCGTTT  1560
 W  M  R   T  Q  P  Q   A  R  A   T  K  Q   Q  A  R  I   N  R  F

TCAAAATCTA AAAAACGATT TACACCAAAC AAGCGATACA AGCGATTTGG AAATGACATT  1620
 Q  N  L   K  N  D  L   H  Q  T   S  D  T   S  D  L  E   M  T  F

TGAAACAAGT CGAATTGGGA AAAAGGTTAT TAATTTTGAA AATGTCTCTT TTTCTTACCC  1680
 E  T  S   R  I  G  K   K  V  I   N  F  E   N  V  S  F   S  Y  P

AGATAAATCT ATCTTGAAAG ACTTTAATTT GTTAATTCAA AATAAAGACC GTATTGGCAT  1740
 D  K  S   I  L  K  D   F  N  L   L  I  Q   N  K  D  R   I  G  I

CGTTGGAGAT AATGGTGTTG GAAAGTCAAC CTTACTTAAT TTAATTGTTC AAGATTTACA  1800
 V  G  D   N  G  V  G   K  S  T   L  L  N   L  I  V  Q   D  L  Q

GCCGGATTCG GGTAATGTCT CTATTGGTGA AACGATACGT GTAGGTTACT TTTCACAACA  1860
 P  D  S   G  N  V  S   I  G  E   T  I  R   V  G  Y  F   S  Q  Q

ACTTCATAAT ATGGATGGCT CAAAACGTGT TATTAATTAT TTGCAAGAGG TTGCAGATGA  1920
 L  H  N   M  D  G  S   K  R  V   I  N  Y   L  Q  E  V   A  D  E

GGTTAAAACT AGTGTCGGTA CAACAAGTGT GACAGAACTA TTGGAACAAT TTCTCTTTCC  1980
 V  K  T   S  V  G  T   T  S  V   T  E  L   L  E  Q  F   L  F  P

ACGTTCGACA CATGGAACAC AAATTGCAAA ATTATCAGGT GGTGAGAAAA AAAGACTTTA  2040
 R  S  T   H  G  T  Q   I  A  K   L  S  G   G  E  K  K   R  L  Y

CCTTTTAAAA ATCCTGATTG AAAAGCCTAA TGTGTTACTA CTTGATGAGC CGACAAATGA  2100
 L  L  K   I  L  I  E   K  P  N   V  L  L   L  D  E  P   T  N  D

CTTAGATATT GCTACATTAA CTGTTCTTGA AAATTTTTTA CAAGGCTTTG GTGGTCCTGT  2160
 L  D  I   A  T  L  T   V  L  E   N  F  L   Q  G  F  G   G  P  V

GATTACAGTT AGTCACGATC GTTACTTTTT AGATAAAGTG GCTAATAAAA TTATTGCGTT  2220
 I  T  V   S  H  D  R   Y  F  L   D  K  V   A  N  K  I   I  A  F

TGAAGATAAC GATATCCGTG AATTTTTTGG TAATTATACT GATTATTTAG ATGAAAAAGC  2280
 E  D  N   D  I  R  E   F  F  G   N  Y  T   D  Y  L  D   E  K  A

ATTTAATGAG CAAAATAATG AAGTTATCAG TAAAAAAGAG AGTACCAAGA CAAGTCGTGA  2340
 F  N  E   Q  N  N  E   V  I  S   K  K  E   S  T  K  T   S  R  E

AAAGCAAAGT CGTAAAAGAA TGTCTTACTT TGAAAAACAA GAATGGGCGA CAATTGAAGA  2400
 K  Q  S   R  K  R  M   S  Y  F   E  K  Q   E  W  A  T   I  E  D

CGATATTATG ATATTGGAAA ATACTATCAC TCGTATAGAA AATGATATGC AAACATGTGG  2460
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 D  I  M   I  L  E  N   T  I  T   R  I  E   N  D  M  Q   T  C  G

TAGTGATTTT ACAAGGTTAT CTGATTTACA AAAGGAATTA GATGCAAAAA ATGAAGCACT   2520
 S  D  F   T  R  L  S   D  L  Q   K  E  L   D  A  K  N   E  A  L

TCTAGAAAAG TATGACCGTT ATGAGTACCT TAGTGAGTTA GACACATGAT TATCCGTCCG   2580
 L  E  K   Y  D  R  Y   E  Y  L   S  E  L   D  T  M  I   I  R  P
                                                 |---->
ATTATTAAAA ATGATGACCA AGCAGTTGCA CAATTAATTC GACAAAGTTT ACGCGCCTAT   2640
 I  I  K  N   D  D  Q   A  V  A   Q  L  I  R   Q  S  L   R  A  Y

GATTTAGATA AACCTGATAC AGCATATTCA GACCCTCACT TAGATCATTT GACCTCATAC   2700
 D  L  D  K   P  D  T   A  Y  S   D  P  H  L   D  H  L   T  S  Y

TACGAAAAAA TAGAGAAGTC AGGATTCTTT GTCATTGAGG AGAGAGATGA GATTATTGGC   2760
 Y  E  K  I   E  K  S   G  F  F   V  I  E  E   R  D  E   I  I  G

TGTGGCGGCT TTGGTCCGCT GAAAAATCTA ATTGCAGAGA TGCAGAAGGT GTACATTGCA   2820
 C  G  G  F   G  P  L   K  N  L   I  A  E  M   Q  K  V   Y  I  A

GAACGTTTCC GTGGTAAGGG GCTTGCTACT GATTTAGTGA AAATGATTGA AGTAGAAGCT   2880
 E  R  F  R   G  K  G   L  A  T   D  L  V  K   M  I  E   V  E  A

CGAAAAATTG GGTATAGACA ACTTTATTTA GAGACAGCCA GTACTTTGAG TAGGGCAACT   2940
 R  K  I  G   Y  R  Q   L  Y  L   E  T  A  S   T  L  S   R  A  T

GCGGTTTATA AGCATATGGG ATATTGTGCC TTATCGCAAC CAATAGCAAA TGATCAAGGT   3000
 A  V  Y  K   H  M  G   Y  C  A   L  S  Q  P   I  A  N   D  Q  G

CATACAGCTA TGGATATTTG GATGATTAAA GATTTATAAG TTGAAAGTGG ATTAGTGAAC   3060
 H  T  A  M   D  I  W   M  I  K   D  L

ATGGATTAAT TATTTTGAGA TAAGAGGAAA GAAAAGGAGA CATATATGGC ATATATTTGG   3120
                                                 M  A   Y  I  W
                                                  |---->
TCTTATTTGA AAAGGTACCC CAATTGGTTA TGGCTTGATT TACTAGGAGC TATGCTTTTT   3180
 S  Y  L  K   R  Y  P   N  W  L   W  L  D  L   L  G  A   M  L  F

GTGACGGTTA TCCTAGGAAT GCCCACAGCC TTAGCGGGTA TGATTGATAA TGGCGTTACA   3240
 V  T  V  I   L  G  M   P  T  A   L  A  G  M   I  D  N   G  V  T

AAAGGTGATC GGACTGGAGT TTATCTGTGG ACGTTCATCA TGTTTATATT TGTTGTACTA   3300
 K  G  D  R   T  G  V   Y  L  W   T  F  I  M   F  I  F   V  V  L

GGTATTATTG GGCGTATTAC GATGGCTTAC GCATCTAGTC GCTTAACGAC AACAATGATT   3360
 G  I  I  G   R  I  T   M  A  Y   A  S  S  R   L  T  T   T  M  I

AGAGATATGC GTAATGATAT GTATGCTAAG CTTCAAGAAT ACTCCCATCA TGAATATGAA   3420
 R  D  M  R   N  D  M   Y  A  K   L  Q  E  Y   S  H  H   E  Y  E

CAGATAGGTG TATCTTCACT AGTGACACGT ATGACAAGCG ATACTTTTGT TTTGATGCAA   3480
 Q  I  G  V   S  S  L   V  T  R   M  T  S  D   T  F  V   L  M  Q

TTTGCTGAAA TGTCTTTACG TTTAGGCCTA GTAACTCCTA TGGTAATGAT TTTTAGCGTG   3540
 F  A  E  M   S  L  R   L  G  L   V  T  P  M   V  M  I   F  S  V

GTTATGATAC TAATTACGAG TCCATCTTTG GCTTGGCTTG TAGCGGTTGC GATGCCTCTT   3600
 V  M  I  L   I  T  S   P  S  L   A  W  L  V   A  V  A   M  P  L

TTGGTAGGAG TCGTTTTATA TGTAGCTATA AAAACAAAAC CTTTATCTGA AAGACAACAG   3660
 L  V  G  V   V  L  Y   V  A  I   K  T  K  P   L  S  E   R  Q  Q
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ACTATGCTTG ATAAAATCAA TCAATATGTT CGTGAAAATT TAACAGGGTT ACGCGTTGTT   3720
T  M  L  D   K  I  N   Q  Y  V   R  E  N  L   T  G  L   R  V  V

AGAGCCTTTG CAAGAGAGAA TTTTCAATCA CAAAAATTTC AAGTCGCTAA CCAACGTTAC   3780
R  A  F  A   R  E  N   F  Q  S   Q  K  F  Q   V  A  N   Q  R  Y

ACAGATACTT CAACTGGTCT TTTTAAATTA ACAGGGCTAA CAGAACCACT TTTCGTTCAA   3840
T  D  T  S   T  G  L   F  K  L   T  G  L  T   E  P  L   F  V  Q

ATTATTATTG CAATGATTGT GGCTATCGTT TGGTTTGCTT TGGATCCCTT ACAAAGAGGT   3900
I  I  I  A   M  I  V   A  I  V   W  F  A  L   D  P  L   Q  R  G

GCTATTAAAA TAGGGGATTT AGTTGCTTTT ATCGAATATA GCTTCCATGC TCTCTTTTCA   3960
A  I  K  I   G  D  L   V  A  F   I  E  Y  S   F  H  A   L  F  S

TTTTTGCTAT TTGCCAATCT TTTTACTATG TATCCTCGTA TGGTGGTATC AAGCCATCGT   4020
F  L  L  F   A  N  L   F  T  M   Y  P  R  M   V  V  S   S  H  R

ATTAGAGAGG TGATGGATAT GCCAATCTCT ATCAATCCTA ATGCCGAAGG TGTTACGGAT   4080
I  R  E  V   M  D  M   P  I  S   I  N  P  N   A  E  G   V  T  D

ACGAAACTTA AAGGGCATTT AGAATTTGAT AATGTAACAT TCGCTTATCC AGGAGAAACA   4140
T  K  L  K   G  H  L   E  F  D   N  V  T  F   A  Y  P   G  E  T

GAGAGTCCCG TTTTGCATGA TATTTCTTTT AAAGCTAAGC CTGGAGAAAC AATTGCTTTT   4200
E  S  P  V   L  H  D   I  S  F   K  A  K  P   G  E  T   I  A  F

ATTGGTTCAA CAGGTTCAGG AAAATCTTCT CTTGTTAATT TGATTCCACG TTTTTATGAT   4260
I  G  S  T   G  S  G   K  S  S   L  V  N  L   I  P  R   F  Y  D

GTGACACTTG GAAAAATCTT AGTAGATGGA GTTGATGTAA GAGATTATAA CCTTAAATCA   4320
V  T  L  G   K  I  L   V  D  G   V  D  V  R   D  Y  N   L  K  S

CTTCGCCAAA AGATTGGATT TATCCCCCAA AAAGCTCTTT TATTTACAGG GACAATAGGA   4380
L  R  Q  K   I  G  F   I  P  Q   K  A  L  L   F  T  G   T  I  G

GAGAATTTAA AATATGGAAA AGCTGATGCT ACTATTGATG ATCTTAGACA AGCGGTTGAT   4440
E  N  L  K   Y  G  K   A  D  A   T  I  D  D   L  R  Q   A  V  D

ATTTCTCAAG CTAAAGAGTT TATTGAGAGT CACCAAGAAG CCTTTGAAAC GCATTTAGCT   4500
I  S  Q  A   K  E  F   I  E  S   H  Q  E  A   F  E  T   H  L  A

GAAGGTGGGA GCAATCTTTC TGGGGGTCAA AAACAACGGT TATCTATTGC TAGGGCTGTT   4560
E  G  G  S   N  L  S   G  G  Q   K  Q  R  L   S  I  A   R  A  V

GTTAAAGATC CAGATTTATA TATTTTTGAT GATTCATTTT CTGCTCTCGA TTATAAGACA   4620
V  K  D  P   D  L  Y   I  F  D   D  S  F  S   A  L  D   Y  K  T

GACGCTACTT TAAGAGCGCG TCTAAAAGAA GTAACCGGTG ATTCTACAGT TTTGATAGTT   4680
D  A  T  L   R  A  R   L  K  E   V  T  G  D   S  T  V   L  I  V

GCTCAAAGGG TGGGTACGAT TATGGATGCT GATCAGATTA TTGTCCTTGA TGAAGGCGAA   4740
A  Q  R  V   G  T  I   M  D  A   D  Q  I  I   V  L  D   E  G  E

ATTGTCGGTC GTGGTACCCA CGCTCAATTA ATAGAAAATA ATGCTATTTA TCGTGAAATC   4800
I  V  G  R   G  T  H   A  Q  L   I  E  N  N   A  I  Y   R  E  I

GCTGAGTCAC AACTGAAGAA CCAAAACTTA TCAGAAGGAG AGTGATTGTA TGAGAAAAAA   4860
A  E  S  Q   L  K  N   Q  N  L   S  E  G  E            M  R  K  K
                                                         |---->
```

```
ATCTGTTTTT TTGAGATTAT GGTCTTACCT AACTCGCTAC AAAGCTACTC TTTTCTTAGC   4920
 S  V  F   L  R  L  W   S  Y  L   T  R  Y   K  A  T  L   F  L  A

GATTTTTTTG AAAGTTTTAT CTAGTTTTAT GAGTGTTCTG GAGCCTTTTA TTTTAGGGTT   4980
 I  F  L   K  V  L  S   S  F  M   S  V  L   E  P  F  I   L  G  L

AGCGATAACA GAGTTGACTG CTAACCTTGT TGATATGGCT AAGGGAGTTT CTGGGGCAGA   5040
 A  I  T   E  L  T  A   N  L  V   D  M  A   K  G  V  S   G  A  E

ATTGAACGTT CCTTATATTG CTGGTATTTT GATTATTTAT TTTTTCAGAG GTGTTTTCTA   5100
 L  N  V   P  Y  I  A   G  I  L   I  I  Y   F  F  R  G   V  F  Y

TGAATTAGGT TCTTATGGCT CAAATT  (SEQ ID NO:7)                         5126
 E  L  G   S  Y  G  S   N
```

FIG. 2a

NFDIETTTFE AMKKHASLLE KISVERSFIE FDKLLLAPYW RKGMLALIDS 50
HAFNYLPCLK NRELQLSAFL SQLDKDFLFE TSEQAWASLI LSMEVEHTKT 100
FLKKWKTSTH FQKDVEHIVD VYRIREQMGL AKEHLYRYGK TIIKQAEGIR 150
KARGLMVDFE KIEQLDSELA IHDRHEIVVN GGTLIKKLGI KPGPQMGDII 200
SQIELAIVLG QLINEEEAIL HFVKQYLMD (SEQ ID NO:8) 229

FIG. 2b

MSDFLVDGLT KSVGDKTVFS NVSFIIHSLD RIGIIGVNGT GKTTLLDVIS 50
GELGFDGDRS PFSSANDYKI AYLKQEPDFD DSQTILDTVL SSDLREMALI 100
KEYELLLNHY EESKQSRLEK VMAEMDSLDA WSIESEVKTV LSKLGITDLQ 150
LSVGELSGGL RRRVQLAQVL LNDADLLLLD EPTNHLDIDT IAWLTNFLKN 200
SKKTVLFITH DRYFLDNVAT RIFELDKAQI TEYQGNYQDY VRLRAEQDER 250
DAASLHKKKQ LYKQELAWMR TQPQARATKQ QARINRFQNL KNDLHQTSDT 300
SDLEMTFETS RIGKKVINFE NVSFSYPDKS ILKDFNLLIQ NKDRIGIVGD 350
NGVGKSTLLN LIVQDLQPDS GNVSIGETIR VGYFSQQLHN MDGSKRVINY 400
LQEVADEVKT SVGTTSVTEL LEQFLFPRST HGTQIAKLSG GEKKRLYLLK 450
ILIEKPNVLL LDEPTNDLDI ATLTVLENFL QGFGGPVITV SHDRYFLDKV 500
ANKIIAFEDN DIREFFGNYT DYLDEKAFNE QNNEVISKKE STKTSREKQS 550
RKRMSYFEKQ EWATIEDDIM ILENTITRIE NDMQTCGSDF TRLSDLQKEL 600
DAKNEALLEK YDRYEYLSEL DT (SEQ ID NO:9) 622

FIG. 2c

MIIRPIIKND DQAVAQLIRQ SLRAYDLDKP DTAYSDPHLD HLTSYYEKIE 50
KSGFFVIEER DEIIGCGGFG PLKNLIAEMQ KVYIAERFRG KGLATDLVKM 100
IEVEARKIGY RQLYLETAST LSRATAVYKH MGYCALSQPI ANDQGHTAMD 150
IWMIKDL (SEQ ID NO:10) 157

FIG. 2d

MAYIWSYLKR YPNWLWLDLL GAMLFVTVIL GMPTALAGMI DNGVTKGDRT 50
GVYLWTFIMF IFVVLGIIGR ITMAYASSRL TTTMIRDMRN DMYAKLQEYS 100
HHEYEQIGVS SLVTRMTSDT FVLMQFAEMS LRLGLVTPMV MIFSVVMILI 150
TSPSLAWLVA VAMPLLVGVV LYVAIKTKPL SERQQTMLDK INQYVRENLT 200
GLRVVRAFAR ENFQSQKFQV ANQRYTDTST GLFKLTGLTE PLFVQIIIAM 250
IVAIVWFALD PLQRGAIKIG DLVAFIEYSF HALFSFLLFA NLFTMYPRMV 300
VSSHRIREVM DMPISINPNA EGVTDTKLKG HLEFDNVTFA YPGETESPVL 350
HDISFKAKPG ETIAFIGSTG SGKSSLVNLI PRFYDVTLGK ILVDGVDVRD 400
YNLKSLRQKI GFIPQKALLF TGTIGENLKY GKADATIDDL RQAVDISQAK 450
EFIESHQEAF ETHLAEGGSN LSGGQKQRLS IARAVVKDPD LYIFDDSFSA 500
LDYKTDATLR ARLKEVTGDS TVLIVAQRVG TIMDADQIIV LDEGEIVGRG 550
THAQLIENNA IYREIAESQL KNQNLSEGE (SEQ ID NO:11) 579

FIG. 2e

MRKKSVFLRL WSYLTRYKAT LFLAIFLKVL SSFMSVLEPF ILGLAITELT 50
ANLVDMAKGV SGAELNVPYI AGILIIYFFR GVFYELGSYG SN 92
(SEQ ID NO:12)

FIG. 2f

```
AATTTGGAAG TGCTCTATCA ACAGTTGAAG TAAAGGAGAT TATTAGTGAA GAAAACATAT    60
 F  G  S   A  L  S   T  V  E  V   K  E  I   I  S  E   E  N  I  W
 ---->
GGTTATATCG GCTCAGTTGC TGCCATTTTA CTAGCTACTC ATATTGGAAG TTACCAACTT   120
 L  Y  R   L  S  C   C  H  F  T   S  Y  S   Y  W  K   L  P  T  W

GGTAAGCATC ATATGGGTCT AGCAACAAAG GACAATCAGA TTGCCTATAT TGATGACAGC   180
             M  G  L   A  T  K   D  N  Q  I   A  Y  I   D  D  S
             |---->
AAAGGTAAGG CAAAAGCCCC TAAAACAAAC AAAACGATGG ATCAAATCAG TGCTGAAGAA   240
K  G  K  A   K  A  P   K  T  N   K  T  M  D   Q  I  S   A  E  E

GGCATCTCTG CTGAACAGAT CGTAGTCAAA ATTACTGACC AAGGCTATGT GACCTCACAC   300
G  I  S  A   E  Q  I   V  V  K   I  T  D  Q   G  Y  V   T  S  H

GGTGACCATT ATCATTTTTA CAATGGGAAA GTTCCTTATG ATGCGATTAT TAGTGAAGAG   360
G  D  H  Y   H  F  Y   N  G  K   V  P  Y  D   A  I  I   S  E  E

TTGTTGATGA CGGATCCTAA TTACCGTTTT AAACAATCAG ACGTTATCAA TGAAATCTTA   420
L  L  M  T   D  P  N   Y  R  F   K  Q  S  D   V  I  N   E  I  L
      |---->
GACGGTTACG TTATTAAAGT CAATGGCAAC TATTATGTTT ACCTCAAGCC AGGTAGTAAG   480
D  G  Y  V   I  K  V   N  G  N   Y  Y  V  Y   L  K  P   G  S  K

CGCAAAAACA TTCGAACCAA ACAACAAATT GCTGAGCAAG TAGCCAAAGG AACTAAAGAA   540
R  K  N  I   R  T  K   Q  Q  I   A  E  Q  V   A  K  G   T  K  E

GCTAAAGAAA AAGGTTTAGC TCAAGTGGCC CATCTCAGTA AAGAAGAAGT TGCGGCAGTC   600
A  K  E  K   G  L  A   Q  V  A   H  L  S  K   E  E  V   A  A  V

AATGAAGCAA AAAGACAAGG ACGCTATACT ACAGACGATG GCTATATTTT TAGTCCGACA   660
N  E  A  K   R  Q  G   R  Y  T   T  D  D  G   Y  I  F   S  P  T

GATATCATTG ATGATTTAGG AGATGCTTAT TTAGTACCTC ATGGTAATCA CTATCATTAT   720
D  I  I  D   D  L  G   D  A  Y   L  V  P  H   G  N  H   Y  H  Y

ATTCCTAAAA AGGATTTGTC TCCAAGTGAG CTAGCTGCTG CACAAGCCTA CTGGAGTCAA   780
I  P  K  K   D  L  S   P  S  E   L  A  A  A   Q  A  Y   W  S  Q

AAACAAGGTC GAGGTGCTAG ACCGTCTGAT TACCGCCCGA CACCAGCCCC AGGTCGTAGG   840
K  Q  G  R   G  A  R   P  S  D   Y  R  P  T   P  A  P   G  R  R

AAAGCCCCAA TTCCTGATGT GACGCCTAAC CCTGGACAAG GTCATCAGCC AGATAACGGT   900
K  A  P  I   P  D  V   T  P  N   P  G  Q  G   H  Q  P   D  N  G

GGCTATCATC CAGCGCCTCC TAGGCCAAAT GATGCGTCAC AAAACAAACA CCAAAGAGAT   960
G  Y  H  P   A  P  P   R  P  N   D  A  S  Q   N  K  H   Q  R  D

GAGTTTAAAG GAAAAACCTT TAAGGAACTT TTAGATCAAC TACACCGTCT TGATTTGAAA  1020
E  F  K  G   K  T  F   K  E  L   L  D  Q  L   H  R  L   D  L  K

TACCGTCATG TGGAAGAAGA TGGGTTGATT TTTGAACCGA CTCAAGTGAT CAAATCAAAC  1080
Y  R  H  V   E  E  D   G  L  I   F  E  P  T   Q  V  I   K  S  N

GCTTTTGGGT ATGTGGTGCC TCATGGAGAT CATTATCATA TTATCCCAAG AAGTCAGTTA  1140
A  F  G  Y   V  V  P   H  G  D   H  Y  H  I   I  P  R   S  Q  L

TCACCTCTTG AAATGGAATT AGCAGATCGA TACTTAGCTG GCCAAACTGA GGACAATGAC  1200
S  P  L  E   M  E  L   A  D  R   Y  L  A  G   Q  T  E   D  N  D

TCAGGTTCAG AGCACTCAAA ACCATCAGAT AAAGAAGTGA CACATACCTT TCTTGGTCAT  1260
```

```
S  G  S  E    H  S  K    P  S  D    K  E  V  T    H  T  F    L  G  H
CGCATCAAAG CTTACGGAAA AGGCTTAGAT GGTAAACCAT ATGATACGAG TGATGCTTAT  1320
R  I  K  A    Y  G  K    G  L  D    G  K  P  Y    D  T  S    D  A  Y
GTTTTTAGTA AAGAATCCAT TCATTCAGTG GATAAATCAG GAGTTACAGC TAAACACGGA  1380
V  F  S  K    E  S  I    H  S  V    D  K  S  G    V  T  A    K  H  G
GATCATTTCC ACTATATAGG ATTTGGAGAA CTTGAACAAT ATGAGTTGGA TGAGGTCGCT  1440
D  H  F  H    Y  I  G    F  G  E    L  E  Q  Y    E  L  D    E  V  A
AACTGGGTGA AAGCAAAAGG TCAAGCTGAT GAGCTTGCTG CTGCTTTGGA TCAGGAACAA  1500
N  W  V  K    A  K  G    Q  A  D    E  L  A  A    A  L  D    Q  E  Q
GGCAAAGAAA AACCACTCTT TGACACTAAA AAAGTGAGTC GCAAAGTAAC AAAAGATGGT  1560
G  K  E  K    P  L  F    D  T  K    K  V  S  R    K  V  T    K  D  G
AAAGTGGGCT ATATGATGCC AAAAGATGGT AAGGACTATT TCTATGCTCG TGATCAACTT  1620
K  V  G  Y    M  M  P    K  D  G    K  D  Y  F    Y  A  R    D  Q  L
GATTTGACTC AGATTGCCTT TGCCGAACAA GAACTAATGC TTAAAGATAA GAAGCATTAC  1680
D  L  T  Q    I  A  F    A  E  Q    E  L  M  L    K  D  K    K  H  Y
CGTTATGACA TTGTTGACAC AGGTATTGAG CCACGACTTG CTGTAGATGT GTCAAGTCTG  1740
R  Y  D  I    V  D  T    G  I  E    P  R  L  A    V  D  V    S  S  L
CCGATGCATG CTGGTAATGC TACTTACGAT ACTGGAAGTT CGTTTGTTAT CCCACATATT  1800
P  M  H  A    G  N  A    T  Y  D    T  G  S  S    F  V  I    P  H  I
GATCATATCC ATGTCGTTCC GTATTCATGG TTGACGCGCG ATCAGATTGC AACAGTCAAG  1860
D  H  I  H    V  V  P    Y  S  W    L  T  R  D    Q  I  A    T  V  K
TATGTGATGC AACACCCCGA AGTTCGTCCG GATGTATGGT CTAAGCCAGG GCATGAAGAG  1920
Y  V  M  Q    H  P  E    V  R  P    D  V  W  S    K  P  G    H  E  E
TCAGGTTCGG TCATTCCAAA TGTTACGCCT CTTGATAAAC GTGCTGGTAT GCCAAACTGG  1980
S  G  S  V    I  P  N    V  T  P    L  D  K  R    A  G  M    P  N  W
CAAATTATCC ATTCTGCTGA AGAAGTTCAA AAAGCCCTAG CAGAAGGTCG TTTTGCAACA  2040
Q  I  I  H    S  A  E    E  V  Q    K  A  L  A    E  G  R    F  A  T
CCAGACGGCT ATATTTTCGA TCCACGAGAT GTTTTGGCCA AAGAAACTTT TGTATGGAAA  2100
P  D  G  Y    I  F  D    P  R  D    V  L  A  K    E  T  F    V  W  K
GATGGCTCCT TTAGCATCCC AAGAGCAGAT GGCAGTTCAT TGAGAACCAT TAATAAATCT  2160
D  G  S  F    S  I  P    R  A  D    G  S  S  L    R  T  I    N  K  S
GATCTATCCC AAGCTGAGTG GCAACAAGCT CAAGAGTTAT TGGCAAAGAA AAATACTGGT  2220
D  L  S  Q    A  E  W    Q  Q  A    Q  E  L  L    A  K  K    N  T  G
GATGCTACTG ATACGGATAA ACCCAAAGAA AAGCAACAGG CAGATAAGAG CAATGAAAAC  2280
D  A  T  D    T  D  K    P  K  E    K  Q  Q  A    D  K  S    N  E  N
CAACAGCCAA GTGAAGCCAG TAAAGAAGAA AAAGAATCAG ATGACTTTAT AGACAGTTTA  2340
Q  Q  P  S    E  A  S    K  E  E    K  E  S  D    D  F  I    D  S  L
CCAGACTATG GTCTAGATAG AGCAACCCTA GAAGATCATA TCAATCAATT AGCACAAAAA  2400
P  D  Y  G    L  D  R    A  T  L    E  D  H  I    N  Q  L    A  Q  K
GCTAATATCG ATCCTAAGTA TCTCATTTTC CAACCAGAAG GTGTCCAATT TTATAATAAA  2460
A  N  I  D    P  K  Y    L  I  F    Q  P  E  G    V  Q  F    Y  N  K
```

```
AATGGTGAAT TGGTAACTTA TGATATCAAG ACACTTCAAC AAATAAACCC TTAACCAAAA  2520
N  G  E  L   V  T  Y   D  I  K   T  L  Q  Q   I  N  P

GAAGATCTCA TTGTTAAAGC ACTGCTTTGT CAAAGCAAGT TACGGTGATT TTGAAGTCAT  2580

TCTATGTAAC GAGTAGTGAT AAAAGTTGGA TAATAGCGGT TTTCTTTTGC AAAGAAATGG  2640

TATCCATGTT AGAATAGTAA AAAAAGAGGA GGATTCTTGG ACTAATGTCA AATAAGTAGA  2700

CAGAAAACTG TGTTATTTTA TTGCGTTAAA ATAATTTTCT TCTTTCTGAT TAGGGGTTAG  2760
                   .K   I  A  N  F   Y  N  E   E  K  Q   N  P  T  L

TCCTAGATTA GCCGTATGTG GGTTGTAATT GTTATAAAAA TTCTCAATGT ATTCAAAGCA  2820
 G  L  N   A  T  H   P  N  Y  N   N  Y  F   N  E  I   Y  E  F  C

GTCTAATTGA ACCTGTTTGA TATTTTGATA ATGTTTTCGG TTGATTTGTC TATGCTTTAA  2880
 D  L  Q   V  Q  K   I  N  Q  Y   H  K  R   N  I  Q   R  H  K  L

ATACTTGAAA AATGCTTCAG TTACGGCATT ATCATAAGGA TATCCAGGAT TAGAAAAAGA  2940
 Y  K  F   F  A  E   T  V  A  N   D  Y  P   Y  G  P   N  S  F  S

ATGCATGATA TTGGCACTGC ACCCTAATAG TGAGACGCAA GAAAAACACT TTTAGGCAAT  3000
 H  M                                                      A  I
<----|
CAGTTTTCTG TACTGTACAG GCGACTGGTC GTTTAATCTC TGTTGAATTC TAGTTTCATT  3060
 L  K  R   Y  Q  V   P  S  Q  D   N  L  R   Q  Q  I   R  T  E  N

ATAAAATGTA ATGTAATTTT TAACAATATT TGTTATACTA TCTTTGTTGT ATTTTCTCCT  3120
 Y  F  T   I  Y  N   K  V  I  N   T  I  S   D  K  N   Y  K  R  R

ATTATGGAAA TAAAAGGTTT CAGTCTTTAG GACGGTGTGA AACCATTCAA TACAGGCATT  3180
 N  H  F   Y  F  T   E  T  K  L   V  T  H   F  W  E   I  C  A  N

ATCTGCAGGT GTTCCTTTTC GAGACATTGA GCGGATAATG TCTTTTTCCG TGCAAGCCTG  3240
 D  A  P   T  G  K   R  S  M  S   R  I  I   D  K  E   T  C  A  Q

GTAGTAAGCC ATAGAAGTAT ACACTGAGCC TTGGTCACTG TGTAAGATTG CTCCTTTATT  3300
 Y  Y  A   M
      <----|
TAGGCAATTT TAACTGATTA AGGGTGTCTA GTACAAAATC CGTGTCCTGA CAATCTGAGA  3360
K  P  L  K   L  Q  N   L  T  D   L  V  F  D   T  D  Q   C  D  S

TAGTGTAAGC TATAATTTCT CGGTTATAGA GATTCATAAT TGATGAGAGA TACAATTTAC  3420
I  T  Y  A   I  I  E   R  N  Y   L  N  M  I   S  S  L   Y  L  K

AGTTACCGAA ATATAGGTAG GTAATATCTG TTACGAGCTT TTCCTTAGGC TTATCGGCAT  3480
C  N  G  F   Y  L  Y   T  I  D   T  V  L  K   E  K  P   K  D  A

GGAAATCCCG ACTCAATTTA TTATCTGTTA AATAATAAGC TTTACCCAAA TTGGGAACTT  3540
H  G  D  R   S  L  K   N  D  T   L  Y  Y  A   K  G  L   N  P  V

TCTTGGTACG TGTCCGACAA AGCCAGCCAT TATTTTTCAT GATACGATAG ACTTTCTTTG  3600
K  K  T  R   T  R  C   L  W  G   N  N  K  M   I  R  Y   V  K  K

TATTAACAGT CAATCCGTGG ATTTTTTTGA GCAATCGTGT AATGGTACGA TAGCCATAAA  3660
T  N  V  T   L  G  H   I  K  K   L  L  R  T   I  T  R   Y  G  Y

TAAAGTGATT CTCCATACAG AGCTGTTCAA TTAATTCAAT AAGGTCATCT TTTTTTGCGG  3720
I  F  H  N   E  M
       <----|
```

```
CTTCTCATAC TCCTTTTTCC AACGGTAATA GGTCGACCGC TTGACCTTAA AACAGTCTAG 3780

AATGAAAACT ATCGGGTAGT TGTTTTTATA GTCTTCCACA AGCTTGATAA GACTTACTTT 3840

                                                            . K
ATCGATTTCC TTATCAAGCC TCGATACTTT TTTAAGAGGT CAACCTGTAA TTGTAATTGT 3900
  I  S  K   R  I  L  G  R  Y  K   K  L  L   D  V  Q  L   Q  L  Q

TCCACTTCAG ACAGATGTTC CAAGCCTTTA CCGTAGGTAT ATTGCTTGCC AACACCTTGA 3960
  E  V  E   S  L  H  E   L  G  K   G  Y  T   Y  Q  K  G   V  G  Q

TGAAAACGAT AAAGCTCCTC GTTTTCGTAC CATTTCATCC AAGTATAGAT TTGACTATTA 4020
  H  F  R   Y  L  E  E   N  E  Y   W  K  M   W  T  Y  I   Q  S  N

TTTTTGATGC CTAAAGTCTC CATAATAACT CTGTTAGACT TGCCTGCTTT CTTCATATCG 4080
  N  K  I   G  L  T  E   M  I  V   R  N  S   K  G  A  K   K  M  D

ATGCAAGCCA GCTTAGTTTC CCATGAATAT GCTTTTTTAA CCATAATAAA ACATTCCTGT 4140
  I  C  A   L  K  T  E   W  S  Y   A  K  K   V  M
                                              <----|

TTCTAGTTTA CTAAATTTCA ACAGGAGTGT TTTTCTTTTG TCTCATTTTA GGGATTCAGT 4200

GCCTATTGTT GTCATCAATT ATTTTTCTAA ATTCCCCGGA CTTAAATTGT GACCCTTGGT 4260

CGGAATGAAA GAGAAGTGTT CCTTCAATCT TTCTTTTATT AAGTGAAAAG GCAACACTTT 4320

TCTGTACAAC ATTTATAAAG TGTTTTTCTA GGCAATTAAT CTTTTAGTCA TTGGTGTTTG 4380
                                 . A  I  L   R  K  T   M  P  T  Q

GTAGTTGAGA CTACCATGAA TGCGGTGGTA ATTCCACCAA TGAACATAGT CTTTAGTCTT 4440
  Y  N  L   S  G  H   I  R  H  Y   N  W  W   H  V  Y   D  K  T  K

AAGAGCTAGT TCTTCCAGCA ATTGAAAGGT TTCTTGATAA ACAAATTCAA TTTTGAAAGC 4500
  L  A  L   E  E  L   L  Q  F  T   E  Q  Y   V  F  E   I  K  F  A

ACGATACGTA CTTTCAGCTA CGGCATTGTC ATAAGGATAA CCAGCCTGAC TAAGCGAACG 4560
  R  Y  T   S  E  A   V  A  N  D   Y  P  Y   G  A  Q   S  L  S  R

TGTGATTCCA AAGGCTTCCA ATATTTCATC AATTAACTGA TTATCAAACT CTTTGCCACG 4620
  T  I  G   F  A  E   L  I  E  D   I  L  Q   N  D  F   E  K  G  R

ATCTGAATGG AACATCTTGA CTTTGGTCAG GGCGTAAGGG ATGCTTTGTA TGGCTTGCTT 4680
  D  S  H   F  M  K   V  K  T  L   A  Y  P   I  S  Q   I  A  Q  K

AACGAGTTCA GCGGTCTTGT GCCAACCAAG AGACAGGCCG ATGATTTCAC GGTTGTATAG 4740
  V  L  E   A  T  K   H  W  G  L   S  L  G   I  I  E   R  N  Y  L

GTCAATGATG AGGCAAACAT AAGCCCAACG ATTGCCTACA CGAACATAGG TTAAGTCAGT 4800
  D  I  I   L  C  V   Y  A  W  R   N  G  V   R  V  Y   T  L  D  T

GACTAAGGCT TGTAGTGGTC TTTCTTGCTT AAATTGCCTG TCTAAGTGGT TGGGAATAGG 4860
  V  L  A   Q  L  P   R  E  Q  K   F  Q  R   D  L  H   N  P  I  P

GGCTTCATTC TTGCCTCTAG AATGTGGTTT GAAGGTGGCT TTCTGATAAA CAGAAACCAA 4920
  A  E  N   K  G  R   S  H  P  K   F  T  A   K  Q  Y   V  S  V  L

ATTGAGTCGC TTCATAATGC GTCGAATCCG ACGACGTGAA AGTGTGATAC CTTCGTTATT 4980
  N  L  R   K  M  I   R  R  I  R   R  R  S   L  T  I   G  E  N  N

CAAGCATATT TTGATTTTTC TGGATCCGTA TCTAGACTCG CTATCGAGAA AAATTCTTTT 5040
  L  C  I   K  I  K   R  S  G  Y   R  S  E   S  D  L   F  I  R  K
```

```
AATAGTTTCT TCAAACTCCG TTTCAGATAC TGACTCCACG GCTTGATAGT AATAACTTGA  5100
  I  T  E   E  F  E   T  E  S  V   S  E  V   A  Q  Y   Y  Y  S  S

GTGTGGCATA TTCAGCCAGC GACACATCTT TGAAATGCTG TATTTATCCT TATTAGCAGT  5160
  H  P  M   N  L  W   R  C  M  K   S  I  S   Y  K  D   K  N  A  T

GATTATTTCC CTTTTTGTGC CATAATCACC GCTGCTTGCT TTAGGATATC TAATT       5215
  I  I  E   R  K  T   G  Y  D  G   S  S  A   K  P  Y   R  I
(SEQ ID NO:13)                                       <----|
```

FIG. 3a

```
FGSALSTVEV KEIISEENIW LYRLSCCHFT SYSYWKLPTW                     40
(SEQ ID NO:14)
```

FIG. 3b

```
MGLATKDNQI AYIDDSKGKA KAPKTNKTMD QISAEEGISA EQIVVKITDQ   50
GYVTSHGDHY HFYNGKVPYD AIISEELLMT DPNYRFKQSD VINEILDGYV  100
IKVNGNYYVY LKPGSKRKNI RTKQQIAEQV AKGTKEAKEK GLAQVAHLSK  150
EEVAAVNEAK RQGRYTTDDG YIFSPTDIID DLGDAYLVPH GNHYHYIPKK  200
DLSPSELAAA QAYWSQKQGR GARPSDYRPT PAPGRRKAPI PDVTPNPGQG  250
HQPDNGGYHP APPRPNDASQ NKHQRDEFKG KTFKELLDQL HRLDLKYRHV  300
EEDGLIFEPT QVIKSNAFGY VVPHGDHYHI IPRSQLSPLE MELADRYLAG  350
QTEDNDSGSE HSKPSDKEVT HTFLGHRIKA YGKGLDGKPY DTSDAYVFSK  400
ESIHSVDKSG VTAKHGDHFH YIGFGELEQY ELDEVANWVK AKGQADELAA  450
ALDQEQGKEK PLFDTKKVSR KVTKDGKVGY MMPKDGKDYF YARDQLDLTQ  500
IAFAEQELML KDKKHYRYDI VDTGIEPRLA VDVSSLPMHA GNATYDTGSS  550
FVIPHIDHIH VVPYSWLTRD QIATVKYVMQ HPEVRPDVWS KPGHEESGSV  600
IPNVTPLDKR AGMPNWQIIH SAEEVQKALA EGRFATPDGY IFDPRDVLAK  650
ETFVWKDGSF SIPRADGSSL RTINKSDLSQ AEWQQAQELL AKKNTGDATD  700
TDKPKEKQQA DKSNENQQPS EASKEEKESD DFIDSLPDYG LDRATLEDHI  750
NQLAQKANID PKYLIFQPEG VQFYNKNGEL VTYDIKTLQQ INP          793
(SEQ ID NO:15)
```

FIG. 3c

```
MTDPNYRFKQ SDVINEILDG YVIKVNGNYY VYLKPGSKRK NIRTKQQIAE   50
QVAKGTKEAK EKGLAQVAHL SKEEVAAVNE AKRQGRYTTD DGYIFSPTDI  100
IDDLGDAYLV PHGNHYHYIP KKDLSPSELA AAQAYWSQKQ GRGARPSDYR  150
PTPAPGRRKA PIPDVTPNPG QGHQPDNGGY HPAPPRPNDA SQNKHQRDEF  200
KGKTFKELLD QLHRLDLKYR HVEEDGLIFE PTQVIKSNAF GYVVPHGDHY  250
HIIPRSQLSP LEMELADRYL AGQTEDNDSG SEHSKPSDKE VTHTFLGHRI  300
KAYGKGLDGK PYDTSDAYVF SKESIHSVDK SGVTAKHGDH FHYIGFGELE  350
QYELDEVANW VKAKGQADEL AAALDQEQGK EKPLFDTKKV SRKVTKDGKV  400
GYMMPKDGKD YFYARDQLDL TQIAFAEQEL MLKDKKHYRY DIVDTGIEPR  450
LAVDVSSLPM HAGNATYDTG SSFVIPHIDH IHVVPYSWLT RDQIATVKYV  500
MQHPEVRPDV WSKPGHEESG SVIPNVTPLD KRAGMPNWQI IHSAEEVQKA  550
LAEGRFATPD GYIFDPRDVL AKETFVWKDG SFSIPRADGS SLRTINKSDL  600
SQAEWQQAQE LLAKKNTGDA TDTDKPKEKQ QADKSNENQQ PSEASKEEKE  650
SDDFIDSLPD YGLDRATLED HINQLAQKAN IDPKYLIFQP EGVQFYNKNG  700
ELVTYDIKTL QQINP  (SEQ ID NO:16)                        715
```

FIG. 3d

```
MHSFSNPGYP YDNAVTEAFF KYLKHRQINR KHYQNIKQVQ LDCFEYIENF   50
YNNYNPHTAN LGLTPNQKEE NYFNAIK  (SEQ ID NO:17)            77
```

FIG. 3e

```
MAYYQACTEK DIIRSMSRKG TPADNACIEW FHTVLKTETF YFHNRRKYNK   50
DSITNIVKNY ITFYNETRIQ QRLNDQSPVQ YRKLIA  (SEQ ID NO:18)  86
```

FIG. 3f

```
MENHFIYGYR TITRLLKKIH GLTVNTKKVY RIMKNNGWLC RTRTKKVPNL   50
GKAYYLTDNK LSRDFHADKP KEKLVTDITY LYFGNCKLYL SSIMNLYNRE  100
IIAYTISDCQ DTDFVLDTLN QLKLPK  (SEQ ID NO:19)            126
```

FIG. 3g

```
MVKKAYSWET KLACIDMKKA GKSNRVIMET LGIKNNSQIY TWMKWYENEE   50
LYRFHQGVGK QYTYGKGLEH LSEVEQLQLQ VDLLKKYRGL IRKSIK       96
(SEQ ID NO:20)
```

FIG. 3h

```
IRYPKASSGD YGTKREIITA NKDKYSISKM CRWLNMPHSS YYYQAVESVS    50
ETEFEETIKR IFLDSESRYG SRKIKICLNN EGITLSRRRI RRIMKRLNLV   100
SVYQKATFKP HSRGKNEAPI PNHLDRQFKQ ERPLQALVTD LTYVRVGNRW   150
AYVCLIIDLY NREIIGLSLG WHKTAELVKQ AIQSIPYALT KVKMFHSDRG   200
KEFDNQLIDE ILEAFGITRS LSQAGYPYDN AVAESTYRAF KIEFVYQETF   250
QLLEELALKT KDYVHWWNYH RIHGSLNYQT PMTKRLIA (SEQ ID NO:21)288
```

FIG. 3i

```
AATTTGAAAG CAGAATTATC TGTAGAAGAT GAGCAATATA CAGCAACAGT TTATGGTAAA    60
N  L  K  A   E  L  S   V  E  D   E  Q  Y  T   A  T  V   Y  G  K
---->
TCTGCTCATG GTTCAACACC ACAAGAAGGT GTTAATGGGG CGACTTATTT AGCTCTTTAT   120
S  A  H  G   S  T  P   Q  E  G   V  N  G  A   T  Y  L   A  L  Y

CTAAGTCAAT TTGATTTTGA AGGTCCTGCT CGTGCTTTCT TAGATGTTAC AGCCAACATT   180
L  S  Q  F   D  F  E   G  P  A   R  A  F  L   D  V  T   A  N  I

ATTCACGAAG ACTTCTCAGG TGAAAAACTT GGAGTAGCTT ATGAAGATGA CTGTATGGGA   240
I  H  E  D   F  S  G   E  K  L   G  V  A  Y   E  D  D   C  M  G

CCATTGAGCA TGAATGCAGG TGTCTTCCAG TTTGATGAAA CTAATGATGA TAATACTATC   300
P  L  S  M   N  A  G   V  F  Q   F  D  E  T   N  D  D   N  T  I

GCTCTTAATT TCCGTTACCC ACAAGGGACA GATGCTAAAA CTATCCAAAC TAAGCTTGAG   360
A  L  N  F   R  Y  P   Q  G  T   D  A  K  T   I  Q  T   K  L  E

AAACTTAACG GAGTTGAAAA AGTGACTCTT TCTGACCATG AACACACACC ACACTATGTA   420
K  L  N  G   V  E  K   V  T  L   S  D  H  E   H  T  P   H  Y  V

CCTATGGACG ATGAATTAGT ATCAACCTTA CTAGCTGTCT ATGAAAAGCA AACTGGTCTT   480
P  M  D  D   E  L  V   S  T  L   L  A  V  Y   E  K  Q   T  G  L

AAAGGACATG AACAGGTTAT TGGTGGTGGG ACATTTGGTC GCTTACTTGA ACGGGGTGTT   540
K  G  H  E   Q  V  I   G  G  G   T  F  G  R   L  L  E   R  G  V

GCATACGGTG CCATGTTCCC AGGAGATGAA AACACTATGC ATCAAGCTAA TGAGTACATG   600
A  Y  G  A   M  F  P   G  D  E   N  T  M  H   Q  A  N   E  Y  M

CCTTTAGAAA ATATTTTCCG TTCGGCTGCT ATCTACGCAG AAGCTATCTA TGAATTAATC   660
```

```
P  L  E  N   I  F  R   S  A  A   I  Y  A  E   A  I  Y   E  L  I
AAATAAAATA ATCCTTAAAC TAAATATGTG ATCAATGATA AAGGGTGGTG AAGACATGAA  720
K  .

AGTGTCTTTG CCTCTTTTCA TAAGGTTAGA TTTGGAGACT TTATGACTGA CTTGGAAAAA  780
                                             M  T  D   L  E  K
                                             |---->
ATTATTAAAG CAATAAAAAG TGATTCACAG AATCAAAATT ATACAGAAAA TGGTATTGAT  840
I  I  K  A   I  K  S   D  S  Q   N  Q  N  Y   T  E  N   G  I  D

CCTTTGTTTG CTGCTCCTAA AACAGCTAGG ATCAATATTG TTGGCCAAGC ACCTGGTTTA  900
P  L  F  A   A  P  K   T  A  R   I  N  I  V   G  Q  A   P  G  L

AAAACTCAAG AAGCAAGACT CTATTGGAAA GATAAATCTG GAGATCGTCT ACGCCAGTGG  960
K  T  Q  E   A  R  L   Y  W  K   D  K  S  G   D  R  L   R  Q  W

CTTGGAGTTG ATGAAGAGAC ATTTTACCAT TCTGGAAAAT TTGCTGTTTT ACCTTTAGAT  1020
L  G  V  D   E  E  T   F  Y  H   S  G  K  F   A  V  L   P  L  D

TTTTATTACC CAGGCAAAGG AAAATCAGGA GATTTACCCC CTAGAAAAGG TTTTGCGGAG  1080
F  Y  Y  P   G  K  G   K  S  G   D  L  P  P   R  K  G   F  A  E

AAATGGCACC CTCTTATTTT AAAAGAAATG CCTAATGTTC AATTGACCTT GCTAGTTGGT  1140
K  W  H  P   L  I  L   K  E  M   P  N  V  Q   L  T  L   L  V  G

CAGTATGCTC AGAAATATTA TCTTGGAAGC TCCGCACATA AAAATCTAAC AGAAACAGTT  1200
Q  Y  A  Q   K  Y  Y   L  G  S   S  A  H  K   N  L  T   E  T  V

AAAGCTTACA AAGACTATCT ACCCGATTAT TTACCCCTGG TTCACCCATC ACCGCGAAAT  1260
K  A  Y  K   D  Y  L   P  D  Y   L  P  L  V   H  P  S   P  R  N

CAAATTTGGC TAAAGAAGAA TCCATGGTTT GAAAAAGATC TAATCGTTGA TTTACAAAAG  1320
Q  I  W  L   K  K  N   P  W  F   E  K  D  L   I  V  D   L  Q  K

ATAGTAGCAG ATATTTTAAA AGATTAAGGA TAGGAGTTGG TATGAGAGAT AATCATCTAC  1380
I  V  A  D   I  L  K   D  .                  M  R  D   N  H  L  H
                                              |---->
ACACGTATTT TTCCTATGAT TGTCAAACGG CATTTGAGGA CTATATTAAT GGTTTTACAG  1440
 T  Y  F   S  Y  D   C  Q  T  A   F  E  D   Y  I  N   G  F  T  G

GTGAATTTAT CACGACAGAA CATTTTGATT TATCAAATCC TTACACCGGT CAAGACGATG  1500
 E  F  I   T  T  E   H  F  D  L   S  N  P   Y  T  G   Q  D  D  V

TTCCTGATTA TAGTGCTTAT TGTCAAAAAA TAGATTATCT TAATCAGAAA TATGGAAATC  1560
 P  D  Y   S  A  Y   C  Q  K  I   D  Y  L   N  Q  K   Y  G  N  R

GATTTAAAAA AGGAATTGAA ATCGGTTATT TTAAAGATAG GGAATCAGAT ATTTTAGATT  1620
 F  K  K   G  I  E   I  G  Y  F   K  D  R   E  S  D   I  L  D  Y

ATTTAAAAAA TAAAGAATTT GATTTAAAAC TATTGTCAAT CCATCATAAT GGTAGGTATG  1680
 L  K  N   K  E  F   D  L  K  L   L  S  I   H  H  N   G  R  Y  D

ATTATCTGCA AGAAGAAGCT CTGAAAGTAC CAACAAAGGG AGCTTTTAGC AGATTACTTT  1740
 Y  L  Q   E  E  A   L  K  V  P   T  K  G   A  F  S   R  L  L  .

AATCGTATGG AATTTGCCAT AGGCCGTGTG GAAGCGCACG TTTTAGCTCA CTTTGATTAT  1800
GGTTTTCGTA AGTTAAACTT AGATGTAGAA GATTTAAAAC CGTTTGAAAC GCAATTGAAG  1860
CGCATTTTCA TAAAGATGTT ATCTAAGGGG TTAGCTTTTG AACTAAATAC CAAATCCCTT  1920
```

```
TATCTATATG GGAATGAAAA ACTTTATCGC TATGCTTTAG AGATACTCAA ACAGCTTGGT  1980

TGTAAACAAT ACTCTATAGG CTCTGACGGT CATATTCCTG AACATTTTTG TTATGAATTT  2040

GATAGACTTC AAGGTCTGCT AAAGGACTAT CAAATTGATG AAAATCATTT GATATGAGGA  2100

AATTTTTGAT AAAAAAGCTA GGCAATATTG CTTAGCTTTT TTGTAATGCT ATTGATAGTT  2160

TTAGTGAAAA TTTCAAAAAA ATAAAGAAAT CATTTACTTG TTGCAAGCGC TTGCGTAAAT  2220

TGTTATGATT TTATTGGTAA CAATTCATTA AAAAAGGAGA ATGATATGAA AAGAAAAGAC  2280
                                                  M  K   R  K  D
                                                  |---->
TTATTTGGTG ATAAACAAAC TCAATACACG ATTAGAAAGT TAAGTGTTGG AGTAGCTTCA  2340
L  F  G  D  K  Q  T  Q  Y  T  I  R  K  L  S  V  G  V  A  S

GTTACAACAG GGGTATGTAT TTTTCTTCAT AGTCCACAGG TATTTGCTGA AGAAGTAAGT  2400
V  T  T  G  V  C  I  F  L  H  S  P  Q  V  F  A  E  E  V  S

GTTTCTCCTG CAACTACAGC GATTGCAGAG TCGAATATTA ATCAGGTTGA CAACCAACAA  2460
V  S  P  A  T  T  A  I  A  E  S  N  I  N  Q  V  D  N  Q  Q

TCTACTAATT TAAAAGATGA CATAAACTCA AACTCTGAGA CGGTTGTGAC ACCCTCAGAT  2520
S  T  N  L  K  D  D  I  N  S  N  S  E  T  V  V  T  P  S  D

ATGCCGGATA CCAAGCAATT AGTATCAGAT GAAACTGACA CTCAAAAGGG AGTGACAGAG  2580
M  P  D  T  K  Q  L  V  S  D  E  T  D  T  Q  K  G  V  T  E

CCGGATAAGG CGACAAGCCT GCTTGAAGAA AATAAAGGTC CTGTTTCAGA TAAAAATACC  2640
P  D  K  A  T  S  L  L  E  E  N  K  G  P  V  S  D  K  N  T

TTAGATTTAA AAGTAGCACC ATCTACATTG CAAAATACTC CCGACAAAAC TTCTCAAGCT  2700
L  D  L  K  V  A  P  S  T  L  Q  N  T  P  D  K  T  S  Q  A

ATAGGTGCTC CAAGCCCTAC CTTGAAAGTA GCTAATCAAG CTCCACGGAT TGAAAATGGT  2760
I  G  A  P  S  P  T  L  K  V  A  N  Q  A  P  R  I  E  N  G

TACTTTAGGC TACATCTTAA AGAATTGCCT CAAGGTCATC CTGTAGAAAG CACTGGACTT  2820
Y  F  R  L  H  L  K  E  L  P  Q  G  H  P  V  E  S  T  G  L

TGGATATGGG GAGATGTTGA TCAACCGTCT AGTAATTGGC CAAATGGTGC TATCCCTATG  2880
W  I  W  G  D  V  D  Q  P  S  S  N  W  P  N  G  A  I  P  M

ACTGATGCTA AGAAAGATGA TTACGGTTAT TATGTTGATT TTAAATTATC TGAAAAACAA  2940
T  D  A  K  K  D  D  Y  G  Y  Y  V  D  F  K  L  S  E  K  Q

CGAAAACAAA TATCTTTTTT AATTAATAAC AAAGCAGGGA CAAATTTAAG CGGCGATCAT  3000
R  K  Q  I  S  F  L  I  N  N  K  A  G  T  N  L  S  G  D  H

CATATTCCAT TATTACGACC TGAGATGAAC CAAGTTTGGA TTGATGAAAA GTACGGTATA  3060
H  I  P  L  L  R  P  E  M  N  Q  V  W  I  D  E  K  Y  G  I

CATACTTATC AACCCCTCAA AGAAGGGTAT GTCCGTATTA ACTATTTGAG TTCCTCTAGT  3120
H  T  Y  Q  P  L  K  E  G  Y  V  R  I  N  Y  L  S  S  S  S

AACTATGACC ACTTATCAGC ATGGCTCTTT AAAGATGTTG CAACCCCYTC AACAACTTGG  3180
N  Y  D  H  L  S  A  W  L  F  K  D  V  A  T  P  S  T  T  W

CCAGATGGTA GTAATTTTGT GAATCAAGGA CTATATGGAA GGTATATTGA TGTATCACTA  3240
P  D  G  S  N  F  V  N  Q  G  L  Y  G  R  Y  I  D  V  S  L
```

```
AAAACTAACG CCAAAGAGAT TGGTTTTCTA ATCTTAGATG AAAGTAAGAC AGGAGATGCA  3300
 K  T  N  A   K  E  I   G  F  L   I  L  D  E   S  K  T   G  D  A

GTGAAAGTTC AACCCAACGA CTATGTTTTT AGAGATTTAG CTAACCATAA CCAAATTTTT  3360
 V  K  V  Q   P  N  D   Y  V  F   R  D  L  A   N  H  N   Q  I  F

GTAAAAGATA AGGATCCAAA GGTTTATAAT AATCCTTATT ACATTGATCA AGTGCAGCTA  3420
 V  K  D  K   D  P  K   V  Y  N   N  P  Y  Y   I  D  Q   V  Q  L

AAGGATGCCC AACAAATTGA TTTAACAAGT ATTCAAGCAA GTTTTACAAC TCTAGATGGG  3480
 K  D  A  Q   Q  I  D   L  T  S   I  Q  A  S   F  T  T   L  D  G

GTAGATAAAA CTGAAATTTT AAAAGAATTG AAAGTGACTG ATAAAAATCA AAATGCTATA  3540
 V  D  K  T   E  I  L   K  E  L   K  V  T  D   K  N  Q   N  A  I

CAAATTTCTG ATATCACTCT CGATACTAGT AAATCTCTTT TAATAATCAA AGGCGACTTT  3600
 Q  I  S  D   I  T  L   D  T  S   K  S  L  L   I  I  K   G  D  F

AATCCTAAAC AAGGTCATTT CAACATATCT TATAATGGTA ACAATGTCAT GACAAGGCAA  3660
 N  P  K  Q   G  H  F   N  I  S   Y  N  G  N   N  V  M   T  R  Q

TCTTGGGAAT TTAAAGACCA ACTTTATGCT TATAGTGGAA ATTTAGGTGC AGTTCTCAAT  3720
 S  W  E  F   K  D  Q   L  Y  A   Y  S  G  N   L  G  A   V  L  N

CAAGATGGTT CAAAAGTTGA AGCCAGCCTC TGGTCACCGA GTGCTGATAG TGTCACTATG  3780
 Q  D  G  S   K  V  E   A  S  L   W  S  P  S   A  D  S   V  T  M

ATTATTTATG ACAAAGATAA CCAAAACAGG GTTGTAGCGA CTACCCCCCT TGTGAAAAAT  3840
 I  I  Y  D   K  D  N   Q  N  R   V  V  A  T   T  P  L   V  K  N

AATAAAGGTG TTTGGCAGAC GATACTTGAT ACTAAATTAG GTATTAAAAA CTATACTGGT  3900
 N  K  G  V   W  Q  T   I  L  D   T  K  L  G   I  K  N   Y  T  G

TACTATTATC TTTACGAAAT AAAAAGAGGT AAGGATAAGG TTAAGATTTT AGATCCTTAT  3960
 Y  Y  Y  L   Y  E  I   K  R  G   K  D  K  V   K  I  L   D  P  Y

GCAAAGTCAT TAGCAGAGTG GGATAGTAAT ACTGTTAATG ATGATATTAA AACGGCTAAA  4020
 A  K  S  L   A  E  W   D  S  N   T  V  N  D   D  I  K   T  A  K

GCAGCTTTTG TAAATCCAAG TCAACTTGGA CCTCAAAATT TAAGTTTTGC TAAAATTGCT  4080
 A  A  F  V   N  P  S   Q  L  G   P  Q  N  L   S  F  A   K  I  A

AATTTTAAAG GAAGACAAGA TGCTGTTATA TACGAAGCAC ATGTAAGAGA CTTCACTTCT  4140
 N  F  K  G   R  Q  D   A  V  I   Y  E  A  H   V  R  D   F  T  S

GATCGATCTT TGGATGGAAA ATTAAAAAAT CAATTTGGTA CCTTTGCAGC CTTTTCAGAG  4200
 D  R  S  L   D  G  K   L  K  N   Q  F  G  T   F  A  A   F  S  E

AAACTAGATT ATTTACAGAA ATTAGGAGTT ACACACATTC AGCTTTTACC GGTATTGAGT  4260
 K  L  D  Y   L  Q  K   L  G  V   T  H  I  Q   L  L  P   V  L  S

TATTTTTATG TTAATGAAAT GGATAAGTCA CGCTCAACAG CTTACACTTC CTCAGACAAT  4320
 Y  F  Y  V   N  E  M   D  K  S   R  S  T  A   Y  T  S   S  D  N

AATTACAATT GGGGCTATGA CCCACAGAGC TATTTTGCTC TTTCTGGGAT GTATTCAGAG  4380
 N  Y  N  W   G  Y  D   P  Q  S   Y  F  A  L   S  G  M   Y  S  E

AAACCAAAAG ATCCATCAGC ACGTATCGCC GAATTAAAAC AATTAATACA TGATATTCAT  4440
 K  P  K  D   P  S  A   R  I  A   E  L  K  Q   L  I  H   D  I  H
```

```
AAACGTGGCA TGGGGGTTAT ACTTGATGTC GTCTATAATC ACACTGCAAA AACTTATCTC  4500
K  R  G  M   G  V  I   L  D  V   V  Y  N  H   T  A  K   T  Y  L

TTTGAGGATA TAGAACCTAA TTATTATCAC TTTATGAATG AAGATGGTTC ACCAAGAGAA  4560
F  E  D  I   E  P  N   Y  Y  H   F  M  N  E   D  G  S   P  R  E

AGTTTTGGAG GGGGACGTTT AGGAACCACT CATGCAATGA GTCGTCGTGT TTTGGTTGAT  4620
S  F  G  G   G  R  L   G  T  T   H  A  M  S   R  R  V   L  V  D

TCCATTAAAT ATCTTACAAG TGAATTTAAA GTTGATGGTT TCCGTTTTGA TATGATGGGA  4680
S  I  K  Y   L  T  S   E  F  K   V  D  G  F   R  F  D   M  M  G

GATCATGATG CGGCTGCGAT TGAATTAGCT TATAAAGAAG CTAAAGCTAT TAATCCTAAT  4740
D  H  D  A   A  A  I   E  L  A   Y  K  E  A   K  A  I   N  P  N

ATGATTATGA TTGGTGAGGG CTGGAGAACA TTCCAAGGCG ATCAAGGTCA GCCGGTTAAA  4800
M  I  M  I   G  E  G   W  R  T   F  Q  G  D   Q  G  Q   P  V  K

CCAGCTGACC AAGATTGGAT GAAGTCAACC GATACAGTTG GCGTCTTTTC AGATGATATT  4860
P  A  D  Q   D  W  M   K  S  T   D  T  V  G   V  F  S   D  D  I

CGTAATAGCT TGAAATCTGG TTTTCCAAAT GAAGGTACTC CAGCTTTCAT CACAGGTGGC  4920
R  N  S  L   K  S  G   F  P  N   E  G  T  P   A  F  I   T  G  G

CCACAATCTT TACAAGGTAT TTTTAAAAAT ATCAAAGCAC AACCTGGGAA TTTTGAAGCA  4980
P  Q  S  L   Q  G  I   F  K  N   I  K  A  Q   P  G  N   F  E  A

GATTCGCCAG GAGATGTGGT GCAGTATATT GCTGCACATG ATAACCTTAC CTTGCATGAT  5040
D  S  P  G   D  V  V   Q  Y  I   A  A  H  D   N  L  T   L  H  D

GTGATTGCAA AATCAATT    (SEQ ID NO:22)                               5058
V  I  A  K   S  I  .
```

FIG. 4a

```
NLKAELSVED EQYTATVYGK SAHGSTPQEG VNGATYLALY LSQFDFEGPA   50
RAFLDVTANI IHEDFSGEKL GVAYEDDCMG PLSMNAGVFQ FDETNDDNTI  100
ALNFRYPQGT DAKTIQTKLE KLNGVEKVTL SDHEHTPHYV PMDDELVSTL  150
LAVYEKQTGL KGHEQVIGGG TFGRLLERGV AYGAMFPGDE NTMHQANEYM  200
PLENIFRSAA IYAEAIYELI K   (SEQ ID NO:23)                221
```

FIG. 4b

```
MTDLEKIIKA IKSDSQNQNY TENGIDPLFA APKTARINIV GQAPGLKTQE   50
ARLYWKDKSG DRLRQWLGVD EETFYHSGKF AVLPLDFYYP GKGKSGDLPP  100
RKGFAEKWHP LILKEMPNVQ LTLLVGQYAQ KYYLGSSAHK NLTETVKAYK  150
DYLPDYLPLV HPSPRNQIWL KKNPWFEKDL IVDLQKIVAD ILKD        194
(SEQ ID NO:24)
```

FIG. 4c

```
MRDNHLHTYF SYDCQTAFED YINGFTGEFI TTEHFDLSNP YTGQDDVPDY   50
SAYCQKIDYL NQKYGNRFKK GIEIGYFKDR ESDILDYLKN KEFDLKLLSI  100
HHNGRYDYLQ EEALKVPTKG AFSRLL  (SEQ ID NO:25)            126
```

FIG. 4d

```
MKRKDLFGDK QTQYTIRKLS VGVASVTTGV CIFLHSPQVF AEEVSVSPAT   50
TAIAESNINQ VDNQQSTNLK DDINSNSETV VTPSDMPDTK QLVSDETDTQ  100
KGVTEPDKAT SLLEENKGPV SDKNTLDLKV APSTLQNTPD KTSQAIGAPS  150
PTLKVANQAP RIENGYFRLH LKELPQGHPV ESTGLWIWGD VDQPSSNWPN  200
GAIPMTDAKK DDYGYYVDFK LSEKQRKQIS FLINNKAGTN LSGDHHIPLL  250
RPEMNQVWID EKYGIHTYQP LKEGYVRINY LSSSSNYDHL SAWLFKDVAT  300
PSTTWPDGSN FVNQGLYGRY IDVSLKTNAK EIGFLILDES KTGDAVKVQP  350
NDYVFRDLAN HNQIFVKDKD PKVYNNPYYI DQVQLKDAQQ IDLTSIQASF  400
TTLDGVDKTE ILKELKVTDK NQNAIQISDI TLDTSKSLLI IKGDFNPKQG  450
HFNISYNGNN VMTRQSWEFK DQLYAYSGNL GAVLNQDGSK VEASLWSPSA  500
DSVTMIIYDK DNQNRVVATT PLVKNNKGVW QTILDTKLGI KNYTGYYYLY  550
EIKRGKDKVK ILDPYAKSLA EWDSNTVNDD IKTAKAAFVN PSQLGPQNLS  600
FAKIANFKGR QDAVIYEAHV RDFTSDRSLD GKLKNQFGTF AAFSEKLDYL  650
QKLGVTHIQL LPVLSYFYVN EMDKSRSTAY TSSDNNYNWG YDPQSYFALS  700
GMYSEKPKDP SARIAELKQL IHDIHKRGMG VILDVVYNHT AKTYLFEDIE  750
PNYYHFMNED GSPRESFGGG RLGTTHAMSR RVLVDSIKYL TSEFKVDGFR  800
FDMMGDHDAA AIELAYKEAK AINPNMIMIG EGWRTFQGDQ GQPVKPADQD  850
WMKSTDTVGV FSDDIRNSLK SGFPNEGTPA FITGGPQSLQ GIFKNIKAQP  900
GNFEADSPGD VVQYIAAHDN LTLHDVIAKS I  (SEQ ID NO:26)      931
```

FIG. 4e

```
AATTCAAAGT TTGACAGAAG GTCAACTTCG TTCTGATATC CCTGAGTTCC GTGCTGGTGA    60
 I  Q  S    L  T  E  G    Q  L  R    S  D  I    P  E  F  R    A  G  D
 ---->
TACTGTACGT GTTCACGCTA AAGTTGTTGA AGGTACTCGC GAACGTATTC AGATCTTTGA   120
 T  V  R    V  H  A  K    V  V  E    G  T  R    E  R  I  Q    I  F  E

AGGTGTTGTT ATCTCACGTA AAGGTCAAGG AATCTCAGAA ATGTACACAG TACGTAAAAT   180
 G  V  V    I  S  R  K    G  Q  G    I  S  E    M  Y  T  V    R  K  I

TTCTGGTGGT ATCGGTGTAG AGCGTACATT CCCAATTCAC ACTCCTCGTG TTGATAAAAT   240
 S  G  G    I  G  V  E    R  T  F    P  I  H    T  P  R  V    D  K  I

CGAAGTTGTT CGTTATGGTA AAGTACGTCG TGCTAAACTT TACTACTTAC GCGCATTGCA   300
 E  V  V    R  Y  G  K    V  R  R    A  K  L    Y  Y  L  R    A  L  Q

AGGTAAAGCT GCACGTATTA AAGAAATCCG TCGTTAATTT TGATGATCAG ATTTTAAAAA   360

TGCTTGGTTG TTTGAGGATA GTAACTATGT TTTAAAACTG GACAACCAAG ACGTAAAAAA   420

TCTGCCTGTG GGCAGTTTTT TTACTAGGTC CCCTTAGTTC AATGGATATA ACAACTCCCT   480
                                              . H  I  Y    C  S  G

CCTAAGGAGT AATTGCTGGT TCGATTCCGG CAGGGGACAT ATTCATTGCA TGTAAATAGC   540
 G  L  S    Y  N  S  T    R  N  R    C  P  V    Y  E  N  C    T  F  L

GGTTTAGAGC TATTTTGCCC CAAATTTCTC TGATTAAGTT TATCGTTCCT ATCTTTTTGT   600
 P  K  S    S  N  Q  G    L  N  R    Q  N  L    K  D  N  R    D  K  Q

TCTTGTAATT GATGTGCGTA AACTTCTAAA GTGATATTTA AATTCTCGTG ATCTAAAACT   660
 E  Q  L    Q  H  A  Y    V  E  L    T  I  N    L  N  E  H    D  L  V

TGAGAGATGG AAATTAGATA GCTTGCAAAT GTATGCCTGA GAGAGTGCAC TCGTACCTCG   720
 Q  S  I    S  I  L  Y    S  A  F    T  H  R    L  S  H  V    R  V  E

CGACCAGTTA TTTTTCGGAT AGTTTTATTG ACTGCATTAT TTGAAAGTTT GTCGAATAAT   780
 R  G  T    I  K  R  I    T  K  N    V  A  N    N  S  L  K    D  F  L

CTGTCGTTTT TATTTTTTGT AAATTCATGC AAAAAAAATA ATGTATCATT GTCAATTGGT   840
 R  D  N    K  N  K  T    F  E  H    L  F  F    L  T  D  N    D  I  P

ATATTTCTGA TACTACTTTT GTTTTTTGTT GGCAGGTATC TTTGGTTGAA ATGATAATCC   900
 I  N  R    I  S  S  K    N  K  T    P  L  Y    R  Q  N  F    H  Y  D

CAAGTTTTAT TAATTGATAA ATATTTGTTA GTGTAATCAA TATCATTAAC TGTTAAACCT   960
 W  T  K    N  I  S  L    Y  K  N    T  Y  D    I  D  N  V    T  L  G

AAACATTCAG CGAAGCGCAT GCCAGTTTTA GCGATGAGGT ATAACGCTGC ATACGATTGA  1020
 L  C  E    A  F  R  M
                <----|
TGTTGTGATT TTTCTTTACA AATTTTTATC AAGCGTAAGT ATTCATTGGT TTCAAGAAAT  1080

TTTATCTCTA TTTACGCCCC TTATTTTTTG CTTTAACCTT AGTGAATAAA CAAAAATTTT  1140

TTTCTATATA TCCCTCGTGA ACAGCCATGG ATACGCAGGC TTTTACATGT ATGTTAAAAC  1200

GCTTTACTGT ATCTTGCACA TGCGTTTGAC TATAATGATT TATGACTTGT TGATATTTAG  1260
```

TGGAAGTAAT ATTGCAAAGT AATATATTTC CTATTATATG TTTATACGAT ATTCGATATT 1320
CCCACCCGTT GTCGCGTTTA CGGAAATACG CCATTGATAT ACTCCACATT AGCTAAAGAA 1380
CAGGGTGTTC AAGGCTACCT TGATGGAAAA GGCTCTCTTA GAGATATTTG TAAATGGTAT 1440
GATATCTCAA GTCGCTCTGT TCTCCAAAAG TGGATAAAAC GGTATACTAG TGGTGAAGAC 1500
TTGAAAGCCA CTAGTAGAGG ATATAGCCGT ATGAAACAAG GAAGGCAAGC CACATTTGAA 1560
GAACGTGTAG AGATTGTTAA CTACACCATT GCCCATGGGA AAGACTATCA AGCAGCTATT 1620
GAGAAGTTTG GTGTTTCCTA CCAACAAATT TATTCTTGGG TGCGTAAGCT TGAGAAGAAT 1680
GGCTCACAAG GTTTGGTTGA TAGACGTGTG AAAGGGTTGG AGAGTAGGCC TGATTTAACC 1740
GAGATTGAGC AACTTTAACT CAAGATTAAA CAATTGGAGG AACGTAATCG TCTCTTAGAA 1800
ATCGAGGTTA GTTTACTAAA AAAGTTAGAA GACATCAAAC GAGGAAACAG ACGGTAAGAC 1860
TAGGTAAGCA TTTAGCGGAG TTCCAAGTAA TCAAGAATTA TTACGATGAG GAATCTAATG 1920
TGCCTATTCA GGCCTTATGC CAACTCTTGA AGGGGTCTCG TTCAGGCTAT TACAAGTGGC 1980
TCAATCGTCA AAAAACAGAT TTTGAGACAA AAAATACAAA GCTAATGGCT AAAATCAAGG 2040
AACTTCGTAG ACTCTACAAT GGTATCTTAG GTTATCGCCG TATGACAACA TTTATTAATC 2100
GTCAACTTGG GACAACTTAA AACAAGAAAC GGATTCGTTG ATTGATGAAC ATTCTGGGGA 2160
TTAGTTCAGT CATTCGTCGT GTTAGCCATG CTTGTACAAA AGCTGGTGAC AGATTTTACG 2220
AAGAAAATAT TCTTAATCGT GAATTTACAG CCACAGCTCA TAACCAGAAA TGGTGCACAG 2280
ATGTCACCTA TCTTCAATAC GGTCTGGGAG CTAAAGCTTA TCTCAGTGCG ATTAAAGACC 2340
TGTATAACGG TTCTATTATC GCTTATGAGA TTAGTCACAA CAATGAAATC CACTTGTTAT 2400
GAAGACCATT AAAAAGGGGC TAGAGCTCAA TCCAGGAGCC ACACCTATCA TCCATAGCGA 2460
TTGAGGTAGT CAATATACTT CCAAAGAATA CCGTTATATC ATACAACAAG CTGGTCTGAC 2520
CTTATCCATG TCCCGGATTG GCAAATGTAT TGATAATGCA CCAACTGAAA GTTTCTTTGG 2580
GTTTTTCAAG ACTGAGTCTT ACCACCTTAA GAAATACAAC TCTTATGATG AGTTGGTCAA 2640
TGATGTGGCA CGTTATATCG AATTCTACAA CACACAACGT TATCAATCAA AATTAAACAA 2700
CCTGACTCCT CTAGAATTCA GGAATCAGGT TGCATAACTT ATCTTTTATT ATTTGACTGT 2760
CTACTTGACA GGGAGCCGTT CAGATTGCTT AACCTTTCTA AATTTGCTAA AATAGCTACA 2820
AGAAAACGAG CCATTTAATG CTTATTTCTT ATACTGTCTT GCCTCACGCT CTCCTCGACC 2880
AAAAATTGAG CGTGAGGCTT TTTGTTTCAT TAAACGATGA TATTTCCATA TTCATCAGTT 2940
TGTTTTCCGA GAGCCATCAA AGCTTCGATA AGGTCGATAA TTCCAGGAAT AAAGGTAATA 3000
CTAAAAATAA TATATAAAAA AACCTGGCCT ATTTTTCCTG CGTAAAATTT ATGCGCTCCA 3060
ATGCCGCCCA AAAGAACGTT AATAAAACAT AAACTACTAT GTTAGCATAA GACTTTATTT 3120

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TTACAACTGA ATTTCATATA AATGGATTAG AGTAAGGGAT AAAAGAAATT AGCATAGCTC  3180

TTTTGAAAAT AAAAAAATTA ATATAATATG GAAAAAATTT TATTTCATAA ACGTTTCATA  3240

AAAGGTATGT AATCTAGTAT TTAGGCAACA CTATTTTGTC ACTGGTGTCT AGTAACTTAT  3300

AGATTGATAA TTTTACTAGT AAACGTAATT CTTCGCTTTA AGAGTTAAAT GTCTATTTAT  3360

TGTAAGCTAA ATTGGGAGGT GAACTTATGT AAAATTAGAT AGGTACTGTC AAGTACGGGA  3420

TGATTATTGA AACAGCCAGT ATGCATCATA AAATCTGTAT TGCTTAATAA CTATTTCCTT  3480

AACCAGACAT CAGTTCATTG TTTATCATCG CTACCCTAAG TCTAGTTTTT TCAATAGAGC  3540

ATTAGGTAGT TTTTGATAAT AAAACTATAT AAACATGAGA ATTAGATTTC GTATTGCATT  3600

CTTCATAATG AGTTATTTGA GATTTTCCTT TGAATAAATA GATACGAAAT TCAGTAACTT  3660

CATATATAAA CGGCTCTATC ATTGAGATAG TTTGTCAAAT GAAGAAATTT TTAATGGAAA  3720

TAGTTTTAAA AACATTAGTT GTAGGCGATG TAAAAATATT AATCCAGTGG ATGCAATAGT  3780

TGCGGAGTAA AAATAGAGAG GAGTAATTAG GAAGTGATAA AAAATGCTAT AGCATATATT  3840

ACCAGAAAAA AAAATAGAAC ACTTATTATA TTTGCTATTT TAACAATTGT TCTTTCTTGC  3900

TTGTATTCAT GTTTAACAAT AATGAAATCA AGTAATGAAA TAGAAAAGGC TTTATATGAA  3960
                      M  K  S   S  N  E  I   E  K  A   L  Y  E
                      |---->

AGTTCTAATT CTTCAATATC AATTACAAAA AAAGATGGTA AATATTTTAA TATTAATCAA  4020
S  S  N  S   S  I  S  I  T  K   K  D  G  K   Y  F  N   I  N  Q

TTTAAGAATA TTGAAAAAAT AAAAGAGGTT GAAGAAAAAA TATTTCAATA TGATGGATTA  4080
F  K  N  I   E  K  I  K  E  V   E  E  K  I   F  Q  Y   D  G  L

GCAAAATTGA AAGATCTTAA AGTAGTTAGT GGTGAGCAAA GTATAAATAG AGAAGATTTA  4140
A  K  L  K   D  L  K  V  V  S   G  E  Q  S   I  N  R   E  D  L

TCTGACGAAT TTAAAAATGT TGTTTCACTA GAAGCTACAA GTAATACTAA AAGAAATCTT  4200
S  D  E  F   K  N  V  V  S  L   E  A  T  S   N  T  K   R  N  L

TTATTTAGTA GTGGAGTATT TAGTTTTAAA GAAGGAAAAA ATATAGAAGA AAATGATAAG  4260
L  F  S  S   G  V  F  S  F  K   E  G  K  N   I  E  E   N  D  K

AATTCAATTC TTGTTCATGA AGAATTTGCT AAACAAAACA AACTAAAATT GGGTGATGAA  4320
N  S  I  L   V  H  E  E  F  A   K  Q  N  K   L  K  L   G  D  E

ATTGATCTTG AATTACTAGA TACGGAAAAA AGTGGAAAAA TAAAAAGTCA TAAATTTAAA  4380
I  D  L  E   L  L  D  T  E  K   S  G  K  I   K  S  H   K  F  K

ATTATAGGAA TCTTTTCTGG TAAAAAACAG GAAACATATA CAGGATTATC ATCTGATTTT  4440
I  I  G  I   F  S  G  K  K  Q   E  T  Y  T   G  L  S   S  D  F

AGCGAAAATA TGGTTTTTGT AGATTATTCA ACTAGCCAAG AAATATTAAA TAAATCAGAG  4500
S  E  N  M   V  F  V  D  Y  S   T  S  Q  E   I  L  N   K  S  E

AATAATAGAA TTGCAAATAA AATTTTAATG TATTCTGGTA GTTTAGAATC TACAGAGCTT  4560
N  N  R  I   A  N  K  I  L  M   Y  S  G  S   L  E  S   T  E  L

GCCTTAAACA AATTGAAAGA CTTTAAAATT GATAAGTCAA AGTATTCTAT TAAGAAAGAT  4620
```

```
A  L  N  K   L  K  D   F  K  I   D  K  S  K   Y  S  I   K  K  D

AATAAAGCAT TCGAAGAGTC TTTAGAGTCA GTGAGTGGAA TAAAACATAT AATTAAAATA  4680
N  K  A  F   E  E  S   L  E  S   V  S  G  I   K  H  I   I  K  I

ATGACTTATT CGATTATGTT AGGTGGAATA GTTGTTCTTT CATTAATCTT GATTCTATGG  4740
M  T  Y  S   I  M  L   G  G  I   V  V  L  S   L  I  L   I  L  W

TTAAGAGAAA GAATTTATGA AATAGGTATA TTTTTATCTA TTGGAACAAC TAAGATACAA  4800
L  R  E  R   I  Y  E   I  G  I   F  L  S  I   G  T  T   K  I  Q

ATTATAAGGC AATTTATATT TGAGTTAATA TTCATATCAA TACCAAGTAT AATATCCTCC  4860
I  I  R  Q   F  I  F   E  L  I   F  I  S  I   P  S  I   I  S  S

TTATTTTTAG GGAATCTACT ATTAAAAGTA ATTGTAGAAG GATTTATTAA CTCAGAGAAC  4920
L  F  L  G   N  L  L   L  K  V   I  V  E  G   F  I  N   S  E  N

TCAATGATTT TCGGTGGAAG TTTAATAAAT AAAAGCAGTT TTATGTTAAA CATAACAACA  4980
S  M  I  F   G  G  S   L  I  N   K  S  S  F   M  L  N   I  T  T

CTTGCAGAAA GTTATTTAAT ATTAATAAGT ATTATTGTTT TATCAGTTGT AATGGCCTCT  5040
L  A  E  S   Y  L  I   L  I  S   I  I  V  L   S  V  V   M  A  S

TCATTAATAT TATTTAAGAA ACCACAAGAA ATATTATCAA AAATAAGTTA GGAGCAAATA  5100
S  L  I  L   F  K  K   P  Q  E   I  L  S  K   I  S  .

ATGGATATAT TAGAAATAAA GAATGTAAAT TACAGTTACG CAAATTCTAA AGAAAAAGTT  5160
M  D  I  L   E  I  K   N  V  N   Y  S  Y  A   N  S  K   E  K  V
|---->

TTGTCAGGAG TAAATCAAAA ATTTGAACTT GGAAAGTTTT ATGCGATAGT AGGGAAGTCA  5220
L  S  G  V   N  Q  K   F  E  L   G  K  F  Y   A  I  V   G  K  S

GGAACAGGAA AATCCACACT TCTTTCCTTA CTTGCAGGAC TTGATAAAGT TCAAACAGGA  5280
G  T  G  K   S  T  L   L  S  L   L  A  G  L   D  K  V   Q  T  G

AAAATCTTGT TTAAGAATGA AGATATAGAA AAGAAAGGAT ATAGTAATCA CAGAAAAAAT  5340
K  I  L  F   K  N  E   D  I  E   K  K  G  Y   S  N  H   R  K  N

AATATATCTT TGGTATTTCA AAATTATAAT TTAATAGATT ATTTATCGCC GATTGAAAAT  5400
N  I  S  L   V  F  Q   N  Y  N   L  I  D  Y   L  S  P   I  E  N

ATTAGACTAG TAAATAAATC AGTAGATGAG AGTATCTTGT TCGAATTAGG TTTAGATAAA  5460
I  R  L  V   N  K  S   V  D  E   S  I  L  F   E  L  G   L  D  K

AAACAAATAA AAAGAAATGT TATGAAATTA TCTGGTGGTC AGCAACAAAG GGTAGCTATT  5520
K  Q  I  K   R  N  V   M  K  L   S  G  G  Q   Q  Q  R   V  A  I

GCTAGGGCAC TGGTATCAGA TGCCCCAATA ATACTAGCTG ATGAGCCTAC CGGTAACCTA  5580
A  R  A  L   V  S  D   A  P  I   I  L  A  D   E  P  T   G  N  L

GACAGTGTTA CTGCTGGAGA AATAATT     (SEQ ID NO:27)                   5607
D  S  V  T   A  G  E   I  I  .
```

FIG. 5a

```
IQSLTEGQLR SDIPEFRAGD TVRVHAKVVE GTRERIQIFE GVVISRKGQG   50
ISEMYTVRKI SGGIGVERTF PIHTPRVDKI EVVRYGKVRR AKLYYLRALQ  100
GKAARIKEIR R  (SEQ ID NO:28)                            111
```

FIG. 5b

```
MRFAECLGLT VNDIDYTNKY LSINKTWDYH FNQRYLPTKN KSSIRNIPID   50
NDTLFFLHEF TKNKNDRLFD KLSNNAVNKT IRKITGREVR VHSLRHTFAS  100
YLISISQVLD HENLNITLEV YAHQLQEQKD RNDKLNQRNL GQNSSKPLFT  150
CNEYVPCRNR TSNYSLGGSC YIH   (SEQ ID NO:29)             173
```

FIG. 5c

```
MKSSNEIEKA LYESSNSSIS ITKKDGKYFN INQFKNIEKI KEVEEKIFQY   50
DGLAKLKDLK VVSGEQSINR EDLSDEFKNV VSLEATSNTK RNLLFSSGVF  100
SFKEGKNIEE NDKNSILVHE EFAKQNKLKL GDEIDLELLD TEKSGKIKSH  150
KFKIIGIFSG KKQETYTGLS SDFSENMVFV DYSTSQEILN KSENNRIANK  200
ILMYSGSLES TELALNKLKD FKIDKSKYSI KKDNKAFEES LESVSGIKHI  250
IKIMTYSIML GGIVVLSLIL ILWLRERIYE IGIFLSIGTT KIQIIRQFIF  300
ELIFISIPSI ISSLFLGNLL LKVIVEGFIN SENSMIFGGS LINKSSFMLN  350
ITTLAESYLI LISIIVLSVV MASSLILFKK PQEILSKIS              389
(SEQ ID NO:30)
```

FIG. 5d

```
MDILEIKNVN YSYANSKEKV LSGVNQKFEL GKFYAIVGKS GTGKSTLLSL   50
LAGLDKVQTG KILFKNEDIE KKGYSNHRKN NISLVFQNYN LIDYLSPIEN  100
IRLVNKSVDE SILFELGLDK KQIKRNVMKL SGGQQQRVAI ARALVSDAPI  150
ILADEPTGNL DSVTAGEII  (SEQ ID NO:31)                    169
```

FIG. 5e

```
CATATGACAA TATTTTTCAA AGTCTACATC ACTTACTCGC CTGTCGTGGA AAATCTGGCA   60
ATACATTAAT CGACCAATTA GTTGCTGATG GTTTACTTCA TGCAGATAAT CACTACCATT  120
TTTTCAATGG GAAGTCTCTG GCCACTTTCA ATACTAACCA ATTGATTCGC GAAGTTGTCT  180
ATGTTGAAAT ATCCTTAGAT ACTATGTCTA GTGGTGAACA TGATTTAGTA AAAGTTAACA  240
TTATCAGACC CACTACCGAG CATACTATCC CCACGATGAT GACAGCTAGC CCCTATCATC  300
AAGGTATCAA TGATCCTGCC GCAGACCAAA AAACATACCA AATGGAGGGT GCGCTAGCAG  360
TTAAACAGCC TAAACACATA CAAGTTGACA CAAAACCATT TAAAGAAGAA GTAAAACATC  420
CTTCAAAATT ACCCATCAGC CCTGCAACTG AAAGCTTCAC ACACATTGAC AGTTATAGTC  480
TCAATGACTA TTTTCTTTCT CGTGGTTTTG CTAATATATA CGTTTCAGGT GTGGGTACTG  540
CTGGCTCTAC GGGTTTCATG ACCAGTGGGG ATTACCAACA AATACAAAGC TTTAAAGCAG  600
TCATTGATTG GTTAAATGGT AAGGTTACTG CATTCACAAG TCATAAACGA GATAAACAAG  660
TCAAGGCTGA TTGGTCAAAC GGCCTTGTAG CAACCACAGG TAAATCTTAT CTCGGTACCA  720
TGTCAACTGG TTTAGCAACA ACTGGCGTTG AGGGGCTGAA AGTCATTATC GCTGAAGCCG  780
CAATCTCCAC ATGGTATGAT TATTATCGAG AAAATGGGCT TGTGTGTAGT CCAGGCGGCT  840
ACCCCGGTGA AGATTTAGAC GTTTTAACAG AATTAACATA CTCACGAAAC CTCTTAGCTG  900
GTGATTACAT CAAAAACAAC GATTGCTATC AAGCATTGTT AAATGAACAA TCAAAAGCAA  960
TTGACCGTCA AAGTGGGGAT TACAACCAAT ACTGGCATGA CCGTAATTAC CTAACTCACG 1020
TCAATAATGT CAAAAGTCGA GTAGTTTACA CTCATGGACT ACAGGATTGG AATGTTAAGC 1080
CAAGACATGT CTACAAAGTT TTCAATGCAT TGCCTCAAAC CATCAAAAAA CACCTTTTTT 1140
TACATCAAGG TCAACATGTG TATATGCATA ATTGGCAGTC GATTGATTTT CGTGAAAGCA 1200
TGAATGCCTT ACTAAGCCAA GAACTACTTG GCATTGACAA TCATTTCCAA TTAGAAGAGG 1260
TCATTTGGCA AGATAATACT ACTGAGCAAA CTTGGCAAGT TTTAGATGCT TTCGGAGGAA 1320
ACCATCAAGA GCAAATTGGT TTAGGTGATA GTAAAAAACT TATTGATAAC CATTATGACA 1380
AAGAAGCCTT TGATACTTAT TGTAAAGACT TCAATGTGTT CAAAAATGAT CTTTTCAAGG 1440
GAAATAATAA AACCAATCAA ATCACTATTA ATCTTCCTCT AAAGAAAAAT TATCTCCTGA 1500
ATGGACAGTG CAAACTCCAT CTACGTGTTA AAACTAGTGA CAAAAAGGCC ATTTTATCAG 1560
CCCAAATCTT AGACTATGGT CCTAAAAAAC GATTCAAAGA TACACCAACC ATCAAATTCT 1620
TAAACAGCCT TGATAATGGT AAAAATTTTG CCAGAGAAGC TTTACGTGAA CTCCCGTTTA 1680
CTAAAGATCA TTATCGTGTC ATCAGTAAAG GTGTCTTGAA CCTTCAAAAT CGTACAGACT 1740
TACTTACAAT TGAGGCTATC GAGCCAGAAC AATGGTTTGA TATCGAGTTT AGCCTCCAAC 1800
CAAGTATATA TCAATTGAGT AAAGGTGATA ATCTAAGGAT TATCCTTTAT ACAACTGATT 1860
TTGAACATAC CATTCGAGAT AATGCTAGTT ACTCTATAAC AGTAGATTTG AGTCAATCTT 1920
ATTTAACTAT CCCAACTAAT CAAGGAAATT AACTTATGAA ACTTCTTACT AAAGAACGGT 1980
TTGATGATTC TCAACACTTT TGGTACCAGA TCAATTTATT ACAAGAGAGT AACTTCGGAG 2040
CAGTTTTTGA CCATGATAAT AAAAACATTC CACAGGTTGT TGCAACTATT GTTGATGATT 2100
TACAAGGTTC CGGAAGTTCG AATCATTTCT GGTATTTTGG CAATACTACT GATACTTCCA 2160
TCCTTATGAT TGCTCATTTA AATCGAAAAT TCTATATTCA GGTTAATTTA AAGGACTTTG 2220
ACTTTGCACT CAATTTAATA GCTATAAATA ATTGGAAGAG TCTCCTCCAA ACTCAACTTG 2280
AAGCTCTAAA CGATACCCTA GCAATATTTC AATAAATAAG GTAGAATGGA GTGACAAAGC 2340
AACGCGAGGG AGACTGATTA ATGTCATCTT ATTGGAATAA CTATCCTGAA CTTAAAAAAA 2400
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ATATTGATGA AACCAATCAA CTAATTCAAG AAAGAATACA GGTCAGAAAT AAAGATATTG  2460
AAGCGGCGCT AAGCCAACTC ACAGCTGCGG GAGGAAAACA GCTCAGACCA GCATTCTTTT  2520
ACCTTTTTTC TCAACTTGGT AATAAGGAGA ATCAAGATAC TCAGCAACTA AAGAAAATCG  2580
CTGCTTCTTT AGAAATCCTT CACGTTGCTA CATTAATCCA TGATGATGTC ATTGATGACT  2640
CACCACTAAG ACGTGGAAAT ATGACCATTC AAAGCAAGTT TGGCAAAGAC ATCGCAGTTT  2700
ATACTGGGGA TTTACTTTTC ACAGTCTTTT TCGATCTTAT TTTAGAATCT ATGACTGATA  2760
CACCATTTAT GAGGATTAAT GCAAAATCTA TGCGTAAAAT TCTCATGGGA GAATTGGACC  2820
AGATGCACCT TCGTTACAAT CAACAACAAG GTATCCATCA CTATTTACGT GCGATTTCAG  2880
GTAAGACAGC CGAACTCTTT AAATTAGCTA GCAAAGAAGG AGCTTACTTT GGTGGTGCAG  2940
AGAAGGAGGT TGTTCGTCTA GCAGGCCATA TCGGCTTTAA CATTGGTATG ACATTCCAAA  3000
TTTTGGATGA TATCCTGGAT TATACTGCAG ATAAAAAAAC ATTTAATAAG CCTGTCTTAG  3060
AGGATTTAAC ACAAGGCGTT TACAGCCTTC CTCTACTTCT TGCCATTGAA GAAAATCCTG  3120
ATATTTTCAA ACCTATTTTA GATAAAAAAA CAGATATGGC TACTGAAGAC ATGGAAAAAA  3180
TTGCTTATCT CGTCGTTTCC CATAGAGGTG TTGACAAAGC TCGCCATCTA GCTCGTAAAT  3240
TTACTGAGAA AGCTATTAGT GACATAAATA AGCTACCCCA GAACTCTGCA AAAAAACAGT  3300
TGCTACAATT AACTAATTAC CTTTTAAAAC GCAAAATTTA AATAATAAAA AAACATTCCA  3360
CAATGCTAGA AAAGCAGTTA GGGAATGTTT TTTTATTATC ATTTATTTAT CGCACCTATC  3420
AATCATCATA GATCACCATC ATCAGCGGCT TTCAGCTGAC GGTAACGTTG ACTACTTTGA  3480
GACAATTCTT GAGGAGAACC TTCCAACTCT AATTGCCCAT TTTCTATAAA TAAGATACGA  3540
TCAGCATGTT CAATACCTTT TAAGTGATGT GTAATCCAAA CTAAGGTCTT ACCTTCCAAT  3600
TCTTTCATAA ATACCCTTAG TAAGGCTTGT TCAGTAATAG GATCAAGTCC AACAGTTGGC  3660
TCATCTAAGA TAACAATTGG GACATCTTTT AGTAAGATTC TAGCCAAAGC AATTCTATGC  3720
CTTTCGCCAC CTGAAAACCT AAGTCCAGCT TCATCAACCA TTGTATAGAG ACCATCTGAT  3780
AAATCAGTGA CCATCTCTTT CAATCCAACT CGTTCAAGAA CTTTCCATAC ATCTTCTTCA  3840
CTAGCATCTT GGTTTCCAAT GCGAATGTTA TTTAGCAGGG TTGTATTAAA AAGGTAGGGC  3900
GCTTGTTGTA TCACTCCAAT ATAGTTAGAA ATGCAATCAC CAACTATTGA AACATCAGCA  3960
CCGCCTAGGG TAATCTTCCC TTGACTTGCT TTCAAGTCGC CACGAAGTAG ACTAGCTAAG  4020
GTACTCTTGC CAGAACCACT CCGCCCTAAA ATAGCAATTT TTTCTCCTTC TTTAATATCC  4080
AAATCTAAAT GATGCAAAAC CCATTTCTCT TGTGGCTTAT ACTGGAAACT TAAATTCTTG  4140
ACGGAAAAAT CATATGGCTT ATTAGGCAAT T  (SEQ ID NO:32)                 4171
```

FIG. 6a

YDNIFQSLHH LLACRGKSGN TLIDQLVADG LLHADNHYHF FNGKSLATFN 50
TNQLIREVVY VEISLDTMSS GEHDLVKVNI IRPTTEHTIP TMMTASPYHQ 100
GINDPAADQK TYQMEGALAV KQPKHIQVDT KPFKEEVKHP SKLPISPATE 150
SFTHIDSYSL NDYFLSRGFA NIYVSGVGTA GSTGFMTSGD YQQIQSFKAV 200
IDWLNGKVTA FTSHKRDKQV KADWSNGLVA TTGKSYLGTM STGLATTGVE 250
GLKVIIAEAA ISTWYDYYRE NGLVCSPGGY PGEDLDVLTE LTYSRNLLAG 300
DYIKNNDCYQ ALLNEQSKAI DRQSGDYNQY WHDRNYLTHV NNVKSRVVYT 350
HGLQDWNVKP RHVYKVFNAL PQTIKKHLFL HQGQHVYMHN WQSIDFRESM 400
NALLSQELLG IDNHFQLEEV IWQDNTTEQT WQVLDAFGGN HQEQIGLGDS 450
KKLIDNHYDK EAFDTYCKDF NVFKNDLFKG NNKTNQITIN LPLKKNYLLN 500
GQCKLHLRVK TSDKKAILSA QILDYGPKKR FKDTPTIKFL NSLDNGKNFA 550
REALRELPFT KDHYRVISKG VLNLQNRTDL LTIEAIEPEQ WFDIEFSLQP 600
SIYQLSKGDN LRIILYTTDF EHTIRDNASY SITVDLSQSY LTIPTNQGN 649
(SEQ ID NO:33)

FIG. 6b

MKLLTKERFD DSQHFWYQIN LLQESNFGAV FDHDNKNIPQ VVATIVDDLQ 50
GSGSSNHFWY FGNTTDTSIL MIAHLNRKFY IQVNLKDFDF ALNLIAINNW 100
KSLLQTQLEA LNDTLAIFQ (SEQ ID NO:34) 119

FIG. 6c

MSSYWNNYPE LKKNIDETNQ LIQERIQVRN KDIEAALSQL TAAGGKQLRP 50
AFFYLFSQLG NKENQDTQQL KKIAASLEIL HVATLIHDDV IDDSPLRRGN 100
MTIQSKFGKD IAVYTGDLLF TVFFDLILES MTDTPFMRIN AKSMRKILMG 150
ELDQMHLRYN QQQGIHHYLR AISGKTAELF KLASKEGAYF GGAEKEVVRL 200
AGHIGFNIGM TFQILDDILD YTADKKTFNK PVLEDLTQGV YSLPLLLAIE 250
ENPDIFKPIL DKKTDMATED MEKIAYLVVS HRGVDKARHL ARKFTEKAIS 300
DINKLPQNSA KKQLLQLTNY LLKRKI (SEQ ID NO:35) 326

FIG. 6d

```
LPNKPYDFSV KNLSFQYKPQ EKWVLHHLDL DIKEGEKIAI LGRSGSGKST   50
LASLLRGDLK ASQGKITLGG ADVSIVGDCI SNYIGVIQQA PYLFNTTLLN  100
NIRIGNQDAS EEDVWKVLER VGLKEMVTDL SDGLYTMVDE AGLRFSGGER  150
HRIALARILL KDVPIVILDE PTVGLDPITE QALLRVFMKE LEGKTLVWIT  200
HHLKGIEHAD RILFIENGQL ELEGSPQELS QSSQRYRQLK AADDGDL     247
(SEQ ID NO:36)
```

FIG. 6e

AATTCTATTT GGAGGTTTTT CTTGAATAAA TGGTTAGTTA AGGCAAGTTC CTTAGTTGTT 60
TTAGGTGGTA TGGTTTTATC TGCGGGTTCC CGAGTTTTAG CGGATACTTA TGTCCGTCCA 120
ATTGATAATG GTAGAATTAC AACAGGTTTC AATGGTTATC CTGGACATTG TGGGGTGGAT 180
TATGCTGTTC CGACTGGAAC GATTATTAGG GCAGTGGCAG ATGGTACTGT GAAATTTGCA 240
GGAGCTGGAG CCAACTTTTC TTGGATGACA GACTTAGCAG GAAATTGTGT CATGATTCAA 300
CATGCGGATG GAATGCATAG TGGTTACGCT CATATGTCAC GTGTGGTGGC TAGGACTGGG 360
GAAAAAGTCA AACAAGGAGA TATCATCGGT TACGTAGGAG CAACTGGTAT GGCGACGGGA 420
CCTCACCTTC ATTTTGAATT TTTACCAGCT AACCCTAATT TTCAAAATGG TTTCCATGGA 480
CGTATCAATC CAACGTCACT AATTGCTAAC GTTGCGACCT TTAGTGGAAA AACGCAAGCA 540
TCAGCTCCAA GCATTAAGCC ATTACAATCA GCTCCTGTAC AGAATCAATC TAGTAAATTA 600
AAAGTGTATC GAGTAGATGA ATTACAAAAG GTTAATGGTG TTTGGTTAGT CAAAAATAAC 660
ACCCTAACGC CGACTGGGTT TGATTGGAAC GATAATGGTA TACCAGCATC AGAAATTGAT 720
GAGGTTGATG CTAATGGTAA TTTGACAGCT GACCAGGTTC TTCAAAAAGG TGGTTACTTT 780
ATCTTTAATC CTAAAACTCT TAAGACTGTA GAAAAACCCA TCCAAGGAAC AGCTGGTTTA 840
ACTTGGGCTA AGACACGCTT TGCTAATGGT AGTTCAGTTT GGCTTCGCGT TGACAACAGT 900
CAAGAACTGC TTTACAAATA GTTTGAGGTA TTGATTCATT GTTTTAAATG ACAGTTTTGT 960
TACTAACTAA GTACAATTTC TTTAAACCGT CTGAAAATAA TTTTATAGTC CAGTAAAGTG 1020
TGATATTATA GTCTCGGACT AATAAAAAGG AAATAGGAAT TGAAGCAATG AAAATGAATA 1080
AAAAGGTACT ATTGACATCG ACAATGGCAG CTTCGCTATT ATCAGTCGCA AGTGTTCAAG 1140
CACAAGAAAC AGATACGACG TGGACAGCAC GTACTGTTTC AGAGGTAAAG GCTGATTTGG 1200
TAAAGCAAGA CAATAAATCA TCATATACTG TGAAATATGG TGATACACTA AGCGTTATTT 1260
CAGAAGCAAT GTCAATTGAT ATGAATGTCT TAGCAAAAAT TAATAACATT GCAGATATCA 1320
ATCTTATTTA TCCTGAGACA ACACTGACAG TAACTTACGA TCAGAAGAGT CATACTGCCA 1380
CTTCAATGAA AATAGAAACA CCAGCAACAA ATGCTGCTGG TCAAACAACA GCTACTGTGG 1440
ATTTGAAAAC CAATCAAGTT TCTGTTGCAG ACCAAAAAGT TTCTCTCAAT ACAATTTCGG 1500
AAGGTATGAC ACCAGAAGCA GCAACAACGA TTGTTTCGCC AATGAAGACA TATTCTTCTG 1560
CGCCAGCTTT GAAATCAAAA GAAGTATTAG CACAAGAGCA AGCTGTTAGT CAAGCAGCAG 1620
CTAATGAACA GGTATCAACA GCTCCTGTGA AGTCGATTAC TTCAGAAGTT CCAGCAGCTA 1680
AAGAGGAAGT TAAACCAACT CAGACGTCAG TCAGTCAGTC AACAACAGTA TCACCAGCTT 1740
CTGTTGCCGC TGAAACACCA GCTCCAGTAG CTAAAGTAGC ACCGGTAAGA ACTGTAGCAG 1800
CCCCTAGAGT GGCAAGTGTT AAAGTAGTCA CTCCTAAAGT AGAAACTGGT GCATCACCAG 1860
AGCATGTATC AGCTCCAGCA GTTCCTGTGA CTACGACTTC AACAGCTACA GACAGTAAGT 1920
TACAAGCGAC TGAAGTTAAG AGCGTTCCGG TAGCACAAAA AGCTCCAACA GCAACACCGG 1980
TAGCACAACC AGCTTCAACA ACAAATGCAG TAGCTGCACA TCCTGAAAAT GCAGGGCTCC 2040
AACCTCATGT TGCAGCTTAT AAAGAAAAAG TAGCGTCAAC TTATGGAGTT AATGAATTCA 2100
GTACATACCG TGCAGGTGAT CCAGGTGATC ATGGTAAAGG TTTAGCAGTC GACTTTATTG 2160
TAGGTAAAAA CCAAGCACTT GGTAATGAAG TTGCACAGTA CTCTACACAA AATATGGCAG 2220
CAAATAACAT TTCATATGTT ATCTGGCAAC AAAAGTTTTA CTCAAATACA AATAGTATTT 2280
ATGGACCTGC TAATACTTGG AATGCAATGC CAGATCGTGG TGGCGTTACT GCCAACCATT 2340
ATGACCATGT TCACGTATCA TTTAACAAAT AATATAAAAA AGGAAGCTAT TTGGCTTCTT 2400

TTTTATATGC CTTGAATAGA CTTTCAAGGT TCTTATCTAA TTTTTATTAA ATTGAGGAGA 2460
TTAAGCTATA AGTCTGAAAC TACTTTCACG TTAACCGTGA CTAAATCAAA ACGTTAAAAC 2520
TAAAATCTAA GTCTGTAAAG ATTATTGAAA ACGCTTTAAA AACAGATATA ATAAGGTTTG 2580
TAGATATCTA AAATTAAAAA AGATAAGGAA GTGAGAATAT GCCACATCTA AGTAAAGAAG 2640
CTTTTAAAAA GCAAATAAAA AATGGCATTA TTGTGTCATG TCAAGCTTTG CCTGGGGAGC 2700
CTCTTTATAC TGAAAGTGGA GGTGTTATGC CTCTTTTAGC TTTGGCAGCT CAAGAAGCAG 2760
GAGCGGTTGG TATAAGAGCC AATAGTGTCC GCGACATTAA GGAAATTCAA GAAGTTACTA 2820
ATTTACCTAT CATCGGCATT ATTAAACGTG AATATCCTCC ACAAGAACCA TTTATCACTG 2880
CTACGATGAC AGAGGTGGAT CAATTAGCTA GTTTAGATAT TGCAGTAATA GCCTTAGATT 2940
GTACACTTAG AGAGCGTCAT GATGGTTTGA GTGTAGCTGA GTTTATTCAA AAGATAAAAG 3000
GGAAATATCC TGAACAGTTG CTAATGGCTG ATATAAGTAC TTTTGAAGAA GGTAAAAATG 3060
CTTTTGAAGC AGGAGTTGAT TTTGTGGGTA CAACTCTATC TGGATACACA GATTACAGCC 3120
GCCAAGAAGA AGGACCGGAT ATAGAACTCC TTAATAAGCT TTGTCAAGCC GGTATAGATG 3180
TGATTGCGGA AGGTAAAATT CATACTCCTA AGCAAGCTAA TGAAATTAAT CATATAGGTG 3240
TTGCAGGAAT TGTAGTTGGT GGTGCTATCA CTAGACCAAA AGAAATAGCG GAGCGTTTCA 3300
TCTCAGGACT TAGTTAAAAG TGTTACTCAA AAATCAAAAT CAAAATAAAA AAGGGGAATA 3360
GTTATGAGTA TCAAAAAAAG TGTGATTGGT TTTTGCCTCG GAGCTGCAGC ATTATCAATG 3420
TTTGCTTGTG TAGACAGTAG TCAATCTGTT ATGGCTGCCG AGAAGGATAA AGTCGAAATT 3480
(SEQ ID NO:37)

FIG. 7a

NSIWRFFLNK WLVKASSLVV LGGMVLSAGS RVLADTYVRP IDNGRITTGF 50
NGYPGHCGVD YAVPTGTIIR AVADGTVKFA GAGANFSWMT DLAGNCVMIQ 100
HADGMHSGYA HMSRVVARTG EKVKQGDIIG YVGATGMATG PHLHFEFLPA 150
NPNFQNGFHG RINPTSLIAN VATFSGKTQA SAPSIKPLQS APVQNQSSKL 200
KVYRVDELQK VNGVWLVKNN TLTPTGFDWN DNGIPASEID EVDANGNLTA 250
DQVLQKGGYF IFNPKTLKTV EKPIQGTAGL TWAKTRFANG SSVWLRVDNS 300
QELLYK (SEQ ID NO:38) 306

FIG. 7b

MKMNKKVLLT STMAASLLSV ASVQAQETDT TWTARTVSEV KADLVKQDNK 50
SSYTVKYGDT LSVISEAMSI DMNVLAKINN IADINLIYPE TTLTVTYDQK 100
SHTATSMKIE TPATNAAGQT TATVDLKTNQ VSVADQKVSL NTISEGMTPE 150
AATTIVSPMK TYSSAPALKS KEVLAQEQAV SQAAANEQVS TAPVKSITSE 200
VPAAKEEVKP TQTSVSQSTT VSPASVAAET PAPVAKVAPV RTVAAPRVAS 250
VKVVTPKVET GASPEHVSAP AVPVTTTSTA TDSKLQATEV KSVPVAQKAP 300
TATPVAQPAS TTNAVAAHPE NAGLQPHVAA YKEKVASTYG VNEFSTYRAG 350
DPGDHGKGLA VDFIVGKNQA LGNEVAQYST QNMAANNISY VIWQQKFYSN 400
TNSIYGPANT WNAMPDRGGV TANHYDHVHV SFNK (SEQ ID NO:39) 434

FIG. 7c

MPHLSKEAFK KQIKNGIIVS CQALPGEPLY TESGGVMPLL ALAAQEAGAV 50
GIRANSVRDI KEIQEVTNLP IIGIIKREYP PQEPFITATM TEVDQLASLD 100
IAVIALDCTL RERHDGLSVA EFIQKIKGKY PEQLLMADIS TFEEGKNAFE 150
AGVDFVGTTL SGYTDYXRQE EGPDIELLNK LCQAGIDVIA EGKIHTPKQA 200
NEINHIGVAG IVVGGAITRP KEIAERFISG LS (SEQ ID NO:40) 232

FIG. 7d

MSIKKSVIGF CLGAAALSMF ACVDSSQSVM AAEKDKVEI 39
(SEQ ID NO:41)

FIG. 7e

```
ATGAAAATGA ATAAAAAGGT ACTATTGACA TCGACAATGG CAGCTTCGCT   50
ATTATCAGTC GCAAGTGTTC AAGCACAAGA AACAGATACG ACGTGGACAG  100
CACGTACTGT TTCAGAGGTA AAGGCTGATT TGGTAAAGCA AGACAATAAA  150
TCATCATATA CTGTGAAATA TGGTGATACA CTAAGCGTTA TTTCAGAAGC  200
AATGTCAATT GATATGAATG TCTTAGCAAA AATTAATAAC ATTGCAGATA  250
TCAATCTTAT TTATCCTGAG ACAACACTGA CAGTAACTTA CGATCAGAAG  300
AGTCATACTG CCACTTCAAT GAAAATAGAA ACACCAGCAA CAAATGCTGC  350
TGGTCAAACA ACAGCTACTG TGGATTTGAA AACCAATCAA GTTTCTGTTG  400
CAGACCAAAA AGTTTCTCTC AATACAATTT CGGAAGGTAT GACACCAGAA  450
GCAGCAACAA CGATTGTTTC GCCAATGAAG ACATATTCTT CTGCGCCAGC  500
TTTGAAATCA AAAGAAGTAT TAGCACAAGA GCAAGCTGTT AGTCAAGCAG  550
CAGCTAATGA ACAGGTATCA ACAGCTCCTG TGAAGTCGAT TACTTCAGAA  600
GTTCCAGCAG CTAAAGAGGA AGTTAAACCA ACTCAGACGT CAGTCAGTCA  650
GTCAACAACA GTATCACCAG CTTCTGTTGC CGCTGAAACA CCAGCTCCAG  700
TAGCTAAAGT AGCACCGGTA AGAACTGTAG CAGCCCCTAG AGTGGCAAGT  750
GTTAAAGTAG TCACTCCTAA AGTAGAAACT GGTGCATCAC CAGAGCATGT  800
ATCAGCTCCA GCAGTTCCTG TGACTACGAC TTCAACAGCT ACAGACAGTA  850
AGTTACAAGC GACTGAAGTT AAGAGCGTTC CGGTAGCACA AAAAGCTCCA  900
ACAGCAACAC CGGTAGCACA ACCAGCTTCA ACAACAAATG CAGTAGCTGC  950
ACATCCTGAA AATGCAGGGC TCCAACCTCA TGTTGCAGCT TATAAAGAAA 1000
AAGTAGCGTC AACTTATGGA GTTAATGAAT TCAGTACATA CCGTGCAGGT 1050
GATCCAGGTG ATCATGGTAA AGGTTTAGCA GTCGACTTTA TTGTAGGTAA 1100
AAACCAAGCA CTTGGTAATG AAGTTGCACA GTACTCTACA CAAAATATGG 1150
CAGCAAATAA CATTTCATAT GTTATCTGGC AACAAAAGTT TTACTCAAAT 1200
ACAAATAGTA TTTATGGACC TGCTAATACT TGGAATGCAA TGCCAGATCG 1250
TGGTGGCGTT ACTGCCAACC ATTATGACCA TGTTCACGTA TCATTTAACA 1300
AATAA                                                  1305
```

(SEQ ID NO:42)

FIG. 8

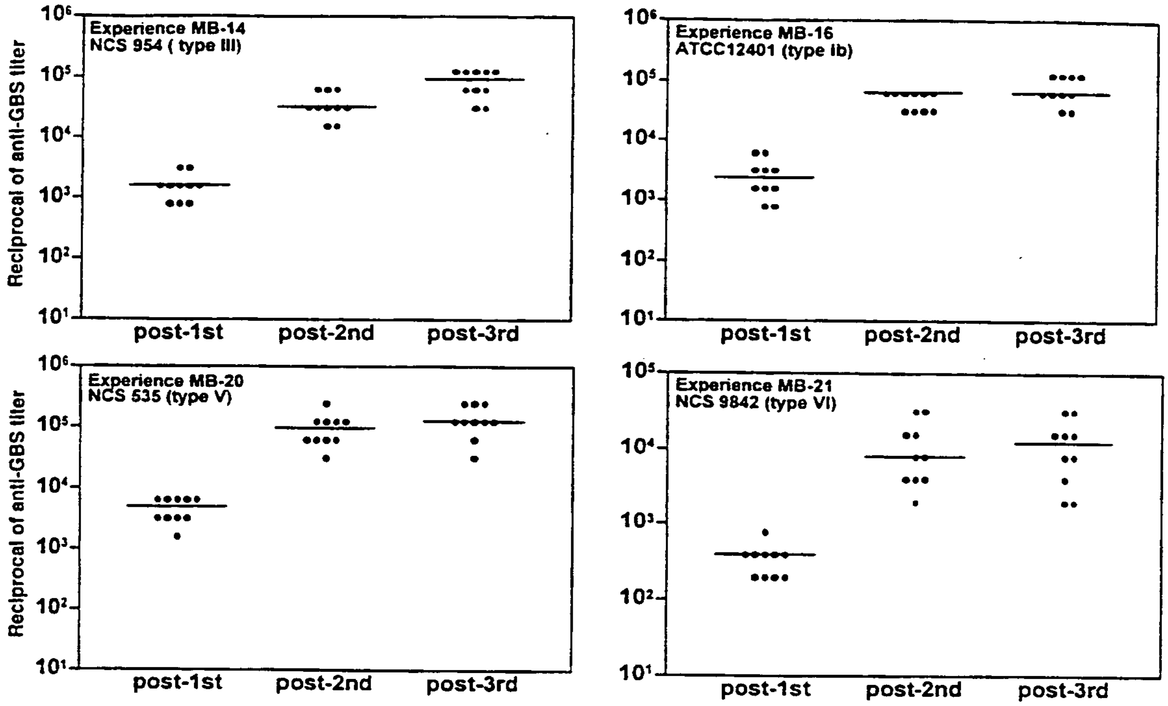
```
CAAGAAACAG ATACGACGTG GACAGCACGT ACTGTTTCAG AGGTAAAGGC    50
TGATTTGGTA AAGCAAGACA ATAAATCATC ATATACTGTG AAATATGGTG   100
ATACACTAAG CGTTATTTCA GAAGCAATGT CAATTGATAT GAATGTCTTA   150
GCAAAAATTA ATAACATTGC AGATATCAAT CTTATTTATC CTGAGACAAC   200
ACTGACAGTA ACTTACGATC AGAAGAGTCA TACTGCCACT TCAATGAAAA   250
TAGAAACACC AGCAACAAAT GCTGCTGGTC AAACAACAGC TACTGTGGAT   300
TTGAAAACCA ATCAAGTTTC TGTTGCAGAC CAAAAAGTTT CTCTCAATAC   350
AATTTCGGAA GGTATGACAC CAGAAGCAGC AACAACGATT GTTTCGCCAA   400
TGAAGACATA TTCTTCTGCG CCAGCTTTGA AATCAAAAGA AGTATTAGCA   450
CAAGAGCAAG CTGTTAGTCA AGCAGCAGCT AATGAACAGG TATCAACAGC   500
TCCTGTGAAG TCGATTACTT CAGAAGTTCC AGCAGCTAAA GAGGAAGTTA   550
AACCAACTCA GACGTCAGTC AGTCAGTCAA CAACAGTATC ACCAGCTTCT   600
GTTGCCGCTG AAACACCAGC TCCAGTAGCT AAAGTAGCAC CGGTAAGAAC   650
TGTAGCAGCC CCTAGAGTGG CAAGTGTTAA AGTAGTCACT CCTAAAGTAG   700
AAACTGGTGC ATCACCAGAG CATGTATCAG CTCCAGCAGT TCCTGTGACT   750
ACGACTTCAA CAGCTACAGA CAGTAAGTTA CAAGCGACTG AAGTTAAGAG   800
CGTTCCGGTA GCACAAAAAG CTCCAACAGC AACACCGGTA GCACAACCAG   850
CTTCAACAAC AAATGCAGTA GCTGCACATC CTGAAAATGC AGGGCTCCAA   900
CCTCATGTTG CAGCTTATAA AGAAAAAGTA GCGTCAACTT ATGGAGTTAA   950
TGAATTCAGT ACATACCGTG CAGGTGATCC AGGTGATCAT GGTAAAGGTT  1000
TAGCAGTCGA CTTTATTGTA GGTAAAAACC AAGCACTTGG TAATGAAGTT  1050
GCACAGTACT CTACACAAAA TATGGCAGCA AATAACATTT CATATGTTAT  1100
CTGGCAACAA AAGTTTTACT CAAATACAAA TAGTATTTAT GGACCTGCTA  1150
ATACTTGGAA TGCAATGCCA GATCGTGGTG GCGTTACTGC CAACCATTAT  1200
GACCATGTTC ACGTATCATT TAACAAATAA     (SEQ ID NO:43)     1230
```

FIG. 9

```
QETDTTWTAR TVSEVKADLV KQDNKSSYTV KYGDTLSVIS EAMSIDMNVL   50
AKINNIADIN LIYPETTLTV TYDQKSHTAT SMKIETPATN AAGQTTATVD  100
LKTNQVSVAD QKVSLNTISE GMTPEAATTI VSPMKTYSSA PALKSKEVLA  150
QEQAVSQAAA NEQVSTAPVK SITSEVPAAK EEVKPTQTSV SQSTTVSPAS  200
VAAETPAPVA KVAPVRTVAA PRVASVKVVT PKVETGASPE HVSAPAVPVT  250
TTSTATDSKL QATEVKSVPV AQKAPTATPV AQPASTTNAV AAHPENAGLQ  300
PHVAAYKEKV ASTYGVNEFS TYRAGDPGDH GKGLAVDFIV GKNQALGNEV  350
AQYSTQNMAA NNISYVIWQQ KFYSNTNSIY GPANTWNAMP DRGGVTANHY  400
DHVHVSFNK  (SEQ ID NO:44)                                409
```

FIG. 9a

Fig. 10


Experience MB-14
NCS 954 (type III)
Experience MB-16
ATCC12401 (type Ib)
Experience MB-20
NCS 535 (type V)
Experience MB-21
NCS 9842 (type VI)
Reciprocal of anti-GBS titer
post-1st
post-2nd
post-3rd

SEQUENCE LISTING

<110> BioChem Vaccins
RIOUX, Clément
DENIS, Martin
BRODEUR, Bernard R.
HAMEL, Josée
CHARLEBOIS, Isabelle
BOYER, Martine

<120> NOVEL GROUP B STREPTOCOCCUS ANTIGENS

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<151> 1998-02-20

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<222> (1841)...(4288)

<221> CDS
<222> (2735)...(4288)

<400> 1

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ta tct ggc aaa gag cca gct aat cgt ttt agt tgg gct aaa aat aaa       47
   Ser Gly Lys Glu Pro Ala Asn Arg Phe Ser Trp Ala Lys Asn Lys
    1               5                  10                  15
```

```
tta tta atc aat gga ttc att gca act cta gca gca act atc tta ttt        95
Leu Leu Ile Asn Gly Phe Ile Ala Thr Leu Ala Ala Thr Ile Leu Phe
                 20                  25                  30

ttt gca gtt caa ttc ata ggt ctt aaa cca gat tac cct gga aaa acc       143
Phe Ala Val Gln Phe Ile Gly Leu Lys Pro Asp Tyr Pro Gly Lys Thr
             35                  40                  45

tac ttt att atc cta ttg aca gca tgg act ttg atg gca tta gta act       191
Tyr Phe Ile Ile Leu Leu Thr Ala Trp Thr Leu Met Ala Leu Val Thr
         50                  55                  60

gct tta gtg gga tgg gat aat agg tat ggt tcc ttc ttg tcg tta tta       239
Ala Leu Val Gly Trp Asp Asn Arg Tyr Gly Ser Phe Leu Ser Leu Leu
     65                  70                  75

ata tta tta ttc cag ctt ggt tca agc gca gga act tac cca ata gaa       287
Ile Leu Leu Phe Gln Leu Gly Ser Ser Ala Gly Thr Tyr Pro Ile Glu
 80                  85                  90                  95

ttg agt cct aag ttc ttt caa aca att caa cca ttt tta ccg atg act       335
Leu Ser Pro Lys Phe Phe Gln Thr Ile Gln Pro Phe Leu Pro Met Thr
                100                 105                 110

tac tct gtt tca gga tta aga gag acc atc tcg ttg acg gga gac gtt       383
Tyr Ser Val Ser Gly Leu Arg Glu Thr Ile Ser Leu Thr Gly Asp Val
            115                 120                 125

aac cat caa tgg aga atg cta gta atc ttt tta gta tca tcg atg ata       431
Asn His Gln Trp Arg Met Leu Val Ile Phe Leu Val Ser Ser Met Ile
        130                 135                 140

ctt gct ctt ctt att tat cgt aaa caa gaa gat taatagaaag tatctagtga     484
Leu Ala Leu Leu Ile Tyr Arg Lys Gln Glu Asp
    145                 150

tagactaaca gtatgatatg gtatgtcaaa gtatttagga ggagaagat atg tct act     542
                                                      Met Ser Thr
                                                          155

tta aca ata att att gca aca tta act gct ttg gaa cat ttt tat att       590
Leu Thr Ile Ile Ile Ala Thr Leu Thr Ala Leu Glu His Phe Tyr Ile
        160                 165                 170

atg tat ttg gag acg tta gcc acc cag tca aat atg act ggg aag att       638
Met Tyr Leu Glu Thr Leu Ala Thr Gln Ser Asn Met Thr Gly Lys Ile
    175                 180                 185

ttt agt atg tct aaa gaa gag ttg tca tat tta ccc gtt att aaa ctt       686
Phe Ser Met Ser Lys Glu Glu Leu Ser Tyr Leu Pro Val Ile Lys Leu
190                 195                 200                 205

ttt aag aat caa ggt gta tac aac ggc ttg att ggc cta ttc ctc ctt       734
Phe Lys Asn Gln Gly Val Tyr Asn Gly Leu Ile Gly Leu Phe Leu Leu
                210                 215                 220
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tat ggg tta tat att tca cag aat caa gaa att gta gct gtt ttt tta 782
Tyr Gly Leu Tyr Ile Ser Gln Asn Gln Glu Ile Val Ala Val Phe Leu
225 230 235

atc aat gta ttg cta gtt gct att tat ggt gct ttg aca gtt gat aaa 830
Ile Asn Val Leu Leu Val Ala Ile Tyr Gly Ala Leu Thr Val Asp Lys
240 245 250

aaa atc tta tta aaa cag ggt ggt tta cct ata tta gct ctt tta aca 878
Lys Ile Leu Leu Lys Gln Gly Gly Leu Pro Ile Leu Ala Leu Leu Thr
255 260 265

ttc tta ttt taatactact tagccgttcg atttagttga acggctttta 927
Phe Leu Phe
270

gtaatcattt ttttctcata atacaggtag tttaagtaat ttgtctttaa aaatagtata 987
atataactac gaattcaaag agaggtgact ttgatt atg act gag aac tgg tta 1041
Met Thr Glu Asn Trp Leu
275

cat act aaa gat ggt tca gat att tat tat cgt gtc gtt ggt caa ggt 1089
His Thr Lys Asp Gly Ser Asp Ile Tyr Tyr Arg Val Val Gly Gln Gly
280 285 290

caa ccg att gtt ttt tta cat ggc aat agc tta agt agt cgc tat ttt 1137
Gln Pro Ile Val Phe Leu His Gly Asn Ser Leu Ser Ser Arg Tyr Phe
295 300 305 310

gat aag caa ata gca tat ttt tct aag tat tac caa gtt att gtt atg 1185
Asp Lys Gln Ile Ala Tyr Phe Ser Lys Tyr Tyr Gln Val Ile Val Met
315 320 325

gat agt aga ggg cat ggc aaa agt cat gca aag cta aat acc att agt 1233
Asp Ser Arg Gly His Gly Lys Ser His Ala Lys Leu Asn Thr Ile Ser
330 335 340

ttc agg caa ata gca gtt gac tta aag gat atc tta gtt cat tta gag 1281
Phe Arg Gln Ile Ala Val Asp Leu Lys Asp Ile Leu Val His Leu Glu
345 350 355

att gat aaa gtt ata ttg gta ggc cat agc gat ggt gcc aat tta gct 1329
Ile Asp Lys Val Ile Leu Val Gly His Ser Asp Gly Ala Asn Leu Ala
360 365 370

tta gtt ttt caa acg atg ttt cca ggt atg gtt aga ggg ctt ttg ctt 1377
Leu Val Phe Gln Thr Met Phe Pro Gly Met Val Arg Gly Leu Leu Leu
375 380 385 390

aat tca ggg aac ctg act att cat ggt cag cga tgg tgg gat att ctt 1425
Asn Ser Gly Asn Leu Thr Ile His Gly Gln Arg Trp Trp Asp Ile Leu
395 400 405

tta gta agg att gcc tat aaa ttc ctt cac tat tta ggg aaa ctc ttt 1473
Leu Val Arg Ile Ala Tyr Lys Phe Leu His Tyr Leu Gly Lys Leu Phe
410 415 420

ccg tat atg agg caa aaa gct caa gtt att tcg ctt atg ttg gag gat 1521
Pro Tyr Met Arg Gln Lys Ala Gln Val Ile Ser Leu Met Leu Glu Asp
425 430 435

ttg aag att agt cca gct gat tta cag cat gtg tca act cct gta atg 1569
Leu Lys Ile Ser Pro Ala Asp Leu Gln His Val Ser Thr Pro Val Met
440 445 450

gtt ttg gtt gga aat aag gac ata att aag tta aat cat tct aag aaa 1617
Val Leu Val Gly Asn Lys Asp Ile Ile Lys Leu Asn His Ser Lys Lys
455 460 465 470

ctt gct tct tat ttt cca agg ggg gag ttt tat tct tta gtt ggc ttt 1665
Leu Ala Ser Tyr Phe Pro Arg Gly Glu Phe Tyr Ser Leu Val Gly Phe
475 480 485

ggg cat cac att att aag caa gat tcc cat gtt ttt aat att att gca 1713
Gly His His Ile Ile Lys Gln Asp Ser His Val Phe Asn Ile Ile Ala
490 495 500

aaa aag ttt atc aac gat acg ttg aaa gga gaa att gtt gaa aaa gct 1761
Lys Lys Phe Ile Asn Asp Thr Leu Lys Gly Glu Ile Val Glu Lys Ala
505 510 515

aat tga aaaagtcaaa tcactgactt ctgtgattaa aattgtattt tttatatctg 1817
Asn *

ttttagtgct tattattgtt gaa atg att cat ttg aaa cga act att tct gtt 1870
Met Ile His Leu Lys Arg Thr Ile Ser Val
520 525

gag caa cta aag agt gtt ttt ggg caa tta tct cca atg aat ctt ttc 1918
Glu Gln Leu Lys Ser Val Phe Gly Gln Leu Ser Pro Met Asn Leu Phe
530 535 540 545

tta att atc ctt gtg ggg gtt atc gct gtc tta ccg aca acc gga tat 1966
Leu Ile Ile Leu Val Gly Val Ile Ala Val Leu Pro Thr Thr Gly Tyr
550 555 560

gac ttt gta ctg aat gga ctt tta cgt aca gat aaa agc aaa agg tat 2014
Asp Phe Val Leu Asn Gly Leu Leu Arg Thr Asp Lys Ser Lys Arg Tyr
565 570 575

att tta cag act agt tgg tgt atc aac act ttt aat aac ttg tca gga 2062
Ile Leu Gln Thr Ser Trp Cys Ile Asn Thr Phe Asn Asn Leu Ser Gly
580 585 590

ttc ggt ggc tta atc gat att ggg ttg cgc atg gct ttt tat ggt aaa 2110
Phe Gly Gly Leu Ile Asp Ile Gly Leu Arg Met Ala Phe Tyr Gly Lys
595 600 605

aaa ggt caa gag aag agt gac cta aga gaa gtg act cgt ttt tta ccc 2158
Lys Gly Gln Glu Lys Ser Asp Leu Arg Glu Val Thr Arg Phe Leu Pro
610 615 620 625

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tat ctt att tct ggt ctg tca ttt att agt gtg att gcc tta atc atg     2206
Tyr Leu Ile Ser Gly Leu Ser Phe Ile Ser Val Ile Ala Leu Ile Met
                630                 635                 640

agc cat att ttt cat gcc aaa gct agt gtt gat tac tat tat ttg gta     2254
Ser His Ile Phe His Ala Lys Ala Ser Val Asp Tyr Tyr Tyr Leu Val
            645                 650                 655

tta att ggt gct agt atg tat ttt cct gtt att tat tgg att tct ggt     2302
Leu Ile Gly Ala Ser Met Tyr Phe Pro Val Ile Tyr Trp Ile Ser Gly
        660                 665                 670

cat aaa gga agc cat tat ttc gga gat atg cca tct agt act cgt ata     2350
His Lys Gly Ser His Tyr Phe Gly Asp Met Pro Ser Ser Thr Arg Ile
    675                 680                 685

aaa tta ggt gtt gtt tct ttt ttt gaa tgg gga tgt gcg gcc gca gca     2398
Lys Leu Gly Val Val Ser Phe Phe Glu Trp Gly Cys Ala Ala Ala Ala
690                 695                 700                 705

ttt ata att atc ggt tat tta atg ggc att cat cta cca gtt tat aaa     2446
Phe Ile Ile Ile Gly Tyr Leu Met Gly Ile His Leu Pro Val Tyr Lys
                710                 715                 720

att tta cca cta ttt tgt att ggt tgt gcc gtc ggg att gta tcc ctt     2494
Ile Leu Pro Leu Phe Cys Ile Gly Cys Ala Val Gly Ile Val Ser Leu
            725                 730                 735

att ccc ggt gga tta gga agt ttt gaa tta gtt cta ttt aca ggg ttt     2542
Ile Pro Gly Gly Leu Gly Ser Phe Glu Leu Val Leu Phe Thr Gly Phe
        740                 745                 750

gct gcc gag gga cta cct aaa gaa act gtg gtt gca tgg tta tta ctt     2590
Ala Ala Glu Gly Leu Pro Lys Glu Thr Val Val Ala Trp Leu Leu Leu
    755                 760                 765

tat cgt tta gcc tac tat att att cca ttc ttt gca ggt atc tat ttc     2638
Tyr Arg Leu Ala Tyr Tyr Ile Ile Pro Phe Phe Ala Gly Ile Tyr Phe
770                 775                 780                 785

ttt atc cat tat tta ggt agt caa ata aat caa cgt tat gaa aat gtc     2686
Phe Ile His Tyr Leu Gly Ser Gln Ile Asn Gln Arg Tyr Glu Asn Val
                790                 795                 800

ccg aaa gag tta gta tca act gtt cta caa acc atg gtg agc cat ttg     2734
Pro Lys Glu Leu Val Ser Thr Val Leu Gln Thr Met Val Ser His Leu
            805                 810                 815

atg cgt att tta ggt gca ttc tta ata ttt tca aca gca ttt ttt gaa     2782
Met Arg Ile Leu Gly Ala Phe Leu Ile Phe Ser Thr Ala Phe Phe Glu
        820                 825                 830

aat att act tat att atg tgg ttg cag aag cta ggc ttg gac cca tta     2830
Asn Ile Thr Tyr Ile Met Trp Leu Gln Lys Leu Gly Leu Asp Pro Leu
    835                 840                 845
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caa gaa caa atg tta tgg cag ttt cca ggt tta ttg ctg ggg gtt tgt     2878
Gln Glu Gln Met Leu Trp Gln Phe Pro Gly Leu Leu Leu Gly Val Cys
850                 855                 860                 865

ttt att ctc tta gct aga act att gat caa aaa gtg aaa aat gct ttt     2926
Phe Ile Leu Leu Ala Arg Thr Ile Asp Gln Lys Val Lys Asn Ala Phe
                870                 875                 880

cca att gct att atc tgg att act ttg aca ttg ttt tat ctt aat tta     2974
Pro Ile Ala Ile Ile Trp Ile Thr Leu Thr Leu Phe Tyr Leu Asn Leu
            885                 890                 895

ggt cat att agt tgg cga cta tct ttc tgg ttt att tta cta ttg tta     3022
Gly His Ile Ser Trp Arg Leu Ser Phe Trp Phe Ile Leu Leu Leu Leu
        900                 905                 910

ggc tta tta gtc att aag cca act ctc tat aaa aaa caa ttt att tat     3070
Gly Leu Leu Val Ile Lys Pro Thr Leu Tyr Lys Lys Gln Phe Ile Tyr
    915                 920                 925

agc tgg gaa gag cgt att aag gat gga atc att atc gtt agt tta atg     3118
Ser Trp Glu Glu Arg Ile Lys Asp Gly Ile Ile Ile Val Ser Leu Met
930                 935                 940                 945

gga gtt cta ttt tat att gca gga cta cta ttc cct atc agg gct cat     3166
Gly Val Leu Phe Tyr Ile Ala Gly Leu Leu Phe Pro Ile Arg Ala His
                950                 955                 960

att aca ggt ggt agt att gaa cgc ctg cat tat atc ata gca tgg gag     3214
Ile Thr Gly Gly Ser Ile Glu Arg Leu His Tyr Ile Ile Ala Trp Glu
            965                 970                 975

ccg ata gca ttg gct acg ttg att ctt act ctc gtt tat tta tgt ttg     3262
Pro Ile Ala Leu Ala Thr Leu Ile Leu Thr Leu Val Tyr Leu Cys Leu
        980                 985                 990

gtt aag att tta caa gga aaa tct tgt cag att ggt gat gtg ttc aat     3310
Val Lys Ile Leu Gln Gly Lys Ser Cys Gln Ile Gly Asp Val Phe Asn
    995                 1000                1005

gtg gat cgt tat aaa aaa cta ctt caa gct tac ggt ggt tct tcg gat     3358
Val Asp Arg Tyr Lys Lys Leu Leu Gln Ala Tyr Gly Gly Ser Ser Asp
1010                1015                1020                1025

agc ggt tta gcc ttt tta aat gat aaa agg ctc tac tgg tac caa aaa     3406
Ser Gly Leu Ala Phe Leu Asn Asp Lys Arg Leu Tyr Trp Tyr Gln Lys
                1030                1035                1040

aat gga gaa gat tgc gtt gcg ttc caa ttt gta att gtc aat aat aaa     3454
Asn Gly Glu Asp Cys Val Ala Phe Gln Phe Val Ile Val Asn Asn Lys
            1045                1050                1055

tgt ctt att atg ggg gaa cca gcc ggt gat gac act tat att cgt gaa     3502
Cys Leu Ile Met Gly Glu Pro Ala Gly Asp Asp Thr Tyr Ile Arg Glu
        1060                1065                1070
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gct att gaa tcg ttt att gat gat gct gat aag cta gac tat gac ctt     3550
Ala Ile Glu Ser Phe Ile Asp Asp Ala Asp Lys Leu Asp Tyr Asp Leu
    1075                1080                1085

gtt ttt tac agt att gga cag aag ttg aca cta ctt tta cat gag tat     3598
Val Phe Tyr Ser Ile Gly Gln Lys Leu Thr Leu Leu Leu His Glu Tyr
1090                1095                1100                1105

ggt ttt gac ttt atg aaa gtt ggt gag gat gct tta gtt aat tta gaa     3646
Gly Phe Asp Phe Met Lys Val Gly Glu Asp Ala Leu Val Asn Leu Glu
                1110                1115                1120

acg ttt act ctt aaa ggg aat aag tac aaa cct ttc aga aat gcc cta     3694
Thr Phe Thr Leu Lys Gly Asn Lys Tyr Lys Pro Phe Arg Asn Ala Leu
            1125                1130                1135

aat aga gtt gaa aag gat ggt ttc tat ttc gaa gtt gta caa tcg cca     3742
Asn Arg Val Glu Lys Asp Gly Phe Tyr Phe Glu Val Val Gln Ser Pro
        1140                1145                1150

cat agt caa gag cta cta aat agt ttg gaa gag att tct aat act tgg     3790
His Ser Gln Glu Leu Leu Asn Ser Leu Glu Glu Ile Ser Asn Thr Trp
    1155                1160                1165

tta gaa gga cgt cct gaa aaa ggt ttc tca cta gga tat ttt aat aaa     3838
Leu Glu Gly Arg Pro Glu Lys Gly Phe Ser Leu Gly Tyr Phe Asn Lys
1170                1175                1180                1185

gat tat ttc caa caa gcc cca ata gct ttg gta aaa aat gct gaa cac     3886
Asp Tyr Phe Gln Gln Ala Pro Ile Ala Leu Val Lys Asn Ala Glu His
                1190                1195                1200

gaa gtt gtt gct ttt gct aat att atg cca aac tat gaa aag agt att     3934
Glu Val Val Ala Phe Ala Asn Ile Met Pro Asn Tyr Glu Lys Ser Ile
            1205                1210                1215

atc tct att gat tta atg cgt cac gat aaa cag aaa att ccg aat ggc     3982
Ile Ser Ile Asp Leu Met Arg His Asp Lys Gln Lys Ile Pro Asn Gly
        1220                1225                1230

gtt atg gat ttc ctc ttt tta tca tta ttc tct tat tat caa gag aag     4030
Val Met Asp Phe Leu Phe Leu Ser Leu Phe Ser Tyr Tyr Gln Glu Lys
    1235                1240                1245

gga tac cac tat ttt gat ttg ggg atg gca cct tta tca gga gtt ggt     4078
Gly Tyr His Tyr Phe Asp Leu Gly Met Ala Pro Leu Ser Gly Val Gly
1250                1255                1260                1265

cgc gtt gaa aca agt ttt gct aaa gag aga atg gcg tat ctt gtc tat     4126
Arg Val Glu Thr Ser Phe Ala Lys Glu Arg Met Ala Tyr Leu Val Tyr
                1270                1275                1280

cat ttc ggt agt cat ttc tac tca ttt aat ggt tta cac aag tat aag     4174
His Phe Gly Ser His Phe Tyr Ser Phe Asn Gly Leu His Lys Tyr Lys
            1285                1290                1295
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aag aag ttt aca cca ttg tgg tcg gaa cgt tat att tct tgt tct cgt 4222
Lys Lys Phe Thr Pro Leu Trp Ser Glu Arg Tyr Ile Ser Cys Ser Arg
1300 1305 1310

tcg tcc tgg tta att tgt gct att tgt gcc cta tta atg gaa gat agt 4270
Ser Ser Trp Leu Ile Cys Ala Ile Cys Ala Leu Leu Met Glu Asp Ser
1315 1320 1325

aaa att aag att gtt aaa taagctttat ttggcaatta aaaagagcat 4318
Lys Ile Lys Ile Val Lys
1330 1335

gtcatgcgac atgctctttt taaatcattt aataccattg attgcttgaa tctactttat 4378
aatatgatgt gcttttaaat attgtttagc tactgtagct gctgatttat gctttacagc 4438
tacttggtag ttcatttctt gcatttcttt ttcagtgata tgaccagcaa gtttattgag 4498
agcttttttt acttga 4514

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<213> Streptococcus

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Ser Gly Lys Glu Pro Ala Asn Arg Phe Ser Trp Ala Lys Asn Lys Leu
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Leu Ile Asn Gly Phe Ile Ala Thr Leu Ala Ala Thr Ile Leu Phe Phe
20 25 30
Ala Val Gln Phe Ile Gly Leu Lys Pro Asp Tyr Pro Gly Lys Thr Tyr
35 40 45
Phe Ile Ile Leu Leu Thr Ala Trp Thr Leu Met Ala Leu Val Thr Ala
50 55 60
Leu Val Gly Trp Asp Asn Arg Tyr Gly Ser Phe Leu Ser Leu Leu Ile
65 70 75 80
Leu Leu Phe Gln Leu Gly Ser Ser Ala Gly Thr Tyr Pro Ile Glu Leu
85 90 95
Ser Pro Lys Phe Phe Gln Thr Ile Gln Pro Phe Leu Pro Met Thr Tyr
100 105 110
Ser Val Ser Gly Leu Arg Glu Thr Ile Ser Leu Thr Gly Asp Val Asn
115 120 125
His Gln Trp Arg Met Leu Val Ile Phe Leu Val Ser Ser Met Ile Leu
130 135 140
Ala Leu Leu Ile Tyr Arg Lys Gln Glu Asp
145 150

<210> 3
<211> 118
<212> PRT
<213> Streptococcus

<400> 3
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Phe Tyr Ile Met Tyr Leu Glu Thr Leu Ala Thr Gln Ser Asn Met Thr
20 25 30

Gly Lys Ile Phe Ser Met Ser Lys Glu Glu Leu Ser Tyr Leu Pro Val
35 40 45
Ile Lys Leu Phe Lys Asn Gln Gly Val Tyr Asn Gly Leu Ile Gly Leu
50 55 60
Phe Leu Leu Tyr Gly Leu Tyr Ile Ser Gln Asn Gln Glu Ile Val Ala
65 70 75 80
Val Phe Leu Ile Asn Val Leu Leu Val Ala Ile Tyr Gly Ala Leu Thr
85 90 95
Val Asp Lys Lys Ile Leu Leu Lys Gln Gly Gly Leu Pro Ile Leu Ala
100 105 110
Leu Leu Thr Phe Leu Phe
115

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<211> 247
<212> PRT
<213> Streptococcus

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Met Thr Glu Asn Trp Leu His Thr Lys Asp Gly Ser Asp Ile Tyr Tyr
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Arg Val Val Gly Gln Gly Gln Pro Ile Val Phe Leu His Gly Asn Ser
20 25 30
Leu Ser Ser Arg Tyr Phe Asp Lys Gln Ile Ala Tyr Phe Ser Lys Tyr
35 40 45
Tyr Gln Val Ile Val Met Asp Ser Arg Gly His Gly Lys Ser His Ala
50 55 60
Lys Leu Asn Thr Ile Ser Phe Arg Gln Ile Ala Val Asp Leu Lys Asp
65 70 75 80
Ile Leu Val His Leu Glu Ile Asp Lys Val Ile Leu Val Gly His Ser
85 90 95
Asp Gly Ala Asn Leu Ala Leu Val Phe Gln Thr Met Phe Pro Gly Met
100 105 110
Val Arg Gly Leu Leu Leu Asn Ser Gly Asn Leu Thr Ile His Gly Gln
115 120 125
Arg Trp Trp Asp Ile Leu Leu Val Arg Ile Ala Tyr Lys Phe Leu His
130 135 140
Tyr Leu Gly Lys Leu Phe Pro Tyr Met Arg Gln Lys Ala Gln Val Ile
145 150 155 160
Ser Leu Met Leu Glu Asp Leu Lys Ile Ser Pro Ala Asp Leu Gln His
165 170 175
Val Ser Thr Pro Val Met Val Leu Val Gly Asn Lys Asp Ile Ile Lys
180 185 190
Leu Asn His Ser Lys Lys Leu Ala Ser Tyr Phe Pro Arg Gly Glu Phe
195 200 205
Tyr Ser Leu Val Gly Phe Gly His His Ile Ile Lys Gln Asp Ser His
210 215 220
Val Phe Asn Ile Ile Ala Lys Lys Phe Ile Asn Asp Thr Leu Lys Gly
225 230 235 240
Glu Ile Val Glu Lys Ala Asn
245

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<211> 816
<212> PRT
<213> Streptococcus

<400> 5
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Phe Gly Gln Leu Ser Pro Met Asn Leu Phe Leu Ile Ile Leu Val Gly
20 25 30
Val Ile Ala Val Leu Pro Thr Thr Gly Tyr Asp Phe Val Leu Asn Gly
35 40 45
Leu Leu Arg Thr Asp Lys Ser Lys Arg Tyr Ile Leu Gln Thr Ser Trp
50 55 60
Cys Ile Asn Thr Phe Asn Asn Leu Ser Gly Phe Gly Gly Leu Ile Asp
65 70 75 80
Ile Gly Leu Arg Met Ala Phe Tyr Gly Lys Lys Gly Gln Glu Lys Ser
85 90 95
Asp Leu Arg Glu Val Thr Arg Phe Leu Pro Tyr Leu Ile Ser Gly Leu
100 105 110
Ser Phe Ile Ser Val Ile Ala Leu Ile Met Ser His Ile Phe His Ala
115 120 125
Lys Ala Ser Val Asp Tyr Tyr Tyr Leu Val Leu Ile Gly Ala Ser Met
130 135 140
Tyr Phe Pro Val Ile Tyr Trp Ile Ser Gly His Lys Gly Ser His Tyr
145 150 155 160
Phe Gly Asp Met Pro Ser Ser Thr Arg Ile Lys Leu Gly Val Val Ser
165 170 175
Phe Phe Glu Trp Gly Cys Ala Ala Ala Ala Phe Ile Ile Ile Gly Tyr
180 185 190
Leu Met Gly Ile His Leu Pro Val Tyr Lys Ile Leu Pro Leu Phe Cys
195 200 205
Ile Gly Cys Ala Val Gly Ile Val Ser Leu Ile Pro Gly Gly Leu Gly
210 215 220
Ser Phe Glu Leu Val Leu Phe Thr Gly Phe Ala Ala Glu Gly Leu Pro
225 230 235 240
Lys Glu Thr Val Val Ala Trp Leu Leu Leu Tyr Arg Leu Ala Tyr Tyr
245 250 255
Ile Ile Pro Phe Phe Ala Gly Ile Tyr Phe Phe Ile His Tyr Leu Gly
260 265 270
Ser Gln Ile Asn Gln Arg Tyr Glu Asn Val Pro Lys Glu Leu Val Ser
275 280 285
Thr Val Leu Gln Thr Met Val Ser His Leu Met Arg Ile Leu Gly Ala
290 295 300
Phe Leu Ile Phe Ser Thr Ala Phe Phe Glu Asn Ile Thr Tyr Ile Met
305 310 315 320
Trp Leu Gln Lys Leu Gly Leu Asp Pro Leu Gln Glu Gln Met Leu Trp
325 330 335
Gln Phe Pro Gly Leu Leu Leu Gly Val Cys Phe Ile Leu Leu Ala Arg
340 345 350
Thr Ile Asp Gln Lys Val Lys Asn Ala Phe Pro Ile Ala Ile Ile Trp
355 360 365
Ile Thr Leu Thr Leu Phe Tyr Leu Asn Leu Gly His Ile Ser Trp Arg
370 375 380
Leu Ser Phe Trp Phe Ile Leu Leu Leu Leu Gly Leu Leu Val Ile Lys
385 390 395 400
Pro Thr Leu Tyr Lys Lys Gln Phe Ile Tyr Ser Trp Glu Glu Arg Ile
405 410 415
Lys Asp Gly Ile Ile Ile Val Ser Leu Met Gly Val Leu Phe Tyr Ile
420 425 430

Ala Gly Leu Leu Phe Pro Ile Arg Ala His Ile Thr Gly Gly Ser Ile
435 440 445
Glu Arg Leu His Tyr Ile Ile Ala Trp Glu Pro Ile Ala Leu Ala Thr
450 455 460
Leu Ile Leu Thr Leu Val Tyr Leu Cys Leu Val Lys Ile Leu Gln Gly
465 470 475 480
Lys Ser Cys Gln Ile Gly Asp Val Phe Asn Val Asp Arg Tyr Lys Lys
485 490 495
Leu Leu Gln Ala Tyr Gly Gly Ser Ser Asp Ser Gly Leu Ala Phe Leu
500 505 510
Asn Asp Lys Arg Leu Tyr Trp Tyr Gln Lys Asn Gly Glu Asp Cys Val
515 520 525
Ala Phe Gln Phe Val Ile Val Asn Asn Lys Cys Leu Ile Met Gly Glu
530 535 540
Pro Ala Gly Asp Asp Thr Tyr Ile Arg Glu Ala Ile Glu Ser Phe Ile
545 550 555 560
Asp Asp Ala Asp Lys Leu Asp Tyr Asp Leu Val Phe Tyr Ser Ile Gly
565 570 575
Gln Lys Leu Thr Leu Leu Leu His Glu Tyr Gly Phe Asp Phe Met Lys
580 585 590
Val Gly Glu Asp Ala Leu Val Asn Leu Glu Thr Phe Thr Leu Lys Gly
595 600 605
Asn Lys Tyr Lys Pro Phe Arg Asn Ala Leu Asn Arg Val Glu Lys Asp
610 615 620
Gly Phe Tyr Phe Glu Val Val Gln Ser Pro His Ser Gln Glu Leu Leu
625 630 635 640
Asn Ser Leu Glu Glu Ile Ser Asn Thr Trp Leu Glu Gly Arg Pro Glu
645 650 655
Lys Gly Phe Ser Leu Gly Tyr Phe Asn Lys Asp Tyr Phe Gln Gln Ala
660 665 670
Pro Ile Ala Leu Val Lys Asn Ala Glu His Glu Val Val Ala Phe Ala
675 680 685
Asn Ile Met Pro Asn Tyr Glu Lys Ser Ile Ile Ser Ile Asp Leu Met
690 695 700
Arg His Asp Lys Gln Lys Ile Pro Asn Gly Val Met Asp Phe Leu Phe
705 710 715 720
Leu Ser Leu Phe Ser Tyr Tyr Gln Glu Lys Gly Tyr His Tyr Phe Asp
725 730 735
Leu Gly Met Ala Pro Leu Ser Gly Val Gly Arg Val Glu Thr Ser Phe
740 745 750
Ala Lys Glu Arg Met Ala Tyr Leu Val Tyr His Phe Gly Ser His Phe
755 760 765
Tyr Ser Phe Asn Gly Leu His Lys Tyr Lys Lys Lys Phe Thr Pro Leu
770 775 780
Trp Ser Glu Arg Tyr Ile Ser Cys Ser Arg Ser Ser Trp Leu Ile Cys
785 790 795 800
Ala Ile Cys Ala Leu Leu Met Glu Asp Ser Lys Ile Lys Ile Val Lys
805 810 815

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<212> PRT
<213> Streptococcus

<400> 6

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Asn Ile Thr Tyr Ile Met Trp Leu Gln Lys Leu Gly Leu Asp Pro Leu
20 25 30
Gln Glu Gln Met Leu Trp Gln Phe Pro Gly Leu Leu Leu Gly Val Cys
35 40 45
Phe Ile Leu Leu Ala Arg Thr Ile Asp Gln Lys Val Lys Asn Ala Phe
50 55 60
Pro Ile Ala Ile Ile Trp Ile Thr Leu Thr Leu Phe Tyr Leu Asn Leu
65 70 75 80
Gly His Ile Ser Trp Arg Leu Ser Phe Trp Phe Ile Leu Leu Leu Leu
85 90 95
Gly Leu Leu Val Ile Lys Pro Thr Leu Tyr Lys Lys Gln Phe Ile Tyr
100 105 110
Ser Trp Glu Glu Arg Ile Lys Asp Gly Ile Ile Ile Val Ser Leu Met
115 120 125
Gly Val Leu Phe Tyr Ile Ala Gly Leu Leu Phe Pro Ile Arg Ala His
130 135 140
Ile Thr Gly Gly Ser Ile Glu Arg Leu His Tyr Ile Ile Ala Trp Glu
145 150 155 160
Pro Ile Ala Leu Ala Thr Leu Ile Leu Thr Leu Val Tyr Leu Cys Leu
165 170 175
Val Lys Ile Leu Gln Gly Lys Ser Cys Gln Ile Gly Asp Val Phe Asn
180 185 190
Val Asp Arg Tyr Lys Lys Leu Leu Gln Ala Tyr Gly Gly Ser Ser Asp
195 200 205
Ser Gly Leu Ala Phe Leu Asn Asp Lys Arg Leu Tyr Trp Tyr Gln Lys
210 215 220
Asn Gly Glu Asp Cys Val Ala Phe Gln Phe Val Ile Val Asn Asn Lys
225 230 235 240
Cys Leu Ile Met Gly Glu Pro Ala Gly Asp Asp Thr Tyr Ile Arg Glu
245 250 255
Ala Ile Glu Ser Phe Ile Asp Asp Ala Asp Lys Leu Asp Tyr Asp Leu
260 265 270
Val Phe Tyr Ser Ile Gly Gln Lys Leu Thr Leu Leu Leu His Glu Tyr
275 280 285
Gly Phe Asp Phe Met Lys Val Gly Glu Asp Ala Leu Val Asn Leu Glu
290 295 300
Thr Phe Thr Leu Lys Gly Asn Lys Tyr Lys Pro Phe Arg Asn Ala Leu
305 310 315 320
Asn Arg Val Glu Lys Asp Gly Phe Tyr Phe Glu Val Val Gln Ser Pro
325 330 335
His Ser Gln Glu Leu Leu Asn Ser Leu Glu Glu Ile Ser Asn Thr Trp
340 345 350
Leu Glu Gly Arg Pro Glu Lys Gly Phe Ser Leu Gly Tyr Phe Asn Lys
355 360 365
Asp Tyr Phe Gln Gln Ala Pro Ile Ala Leu Val Lys Asn Ala Glu His
370 375 380
Glu Val Val Ala Phe Ala Asn Ile Met Pro Asn Tyr Glu Lys Ser Ile
385 390 395 400
Ile Ser Ile Asp Leu Met Arg His Asp Lys Gln Lys Ile Pro Asn Gly
405 410 415
Val Met Asp Phe Leu Phe Leu Ser Leu Phe Ser Tyr Tyr Gln Glu Lys
420 425 430
Gly Tyr His Tyr Phe Asp Leu Gly Met Ala Pro Leu Ser Gly Val Gly
435 440 445

Arg Val Glu Thr Ser Phe Ala Lys Glu Arg Met Ala Tyr Leu Val Tyr
450 455 460
His Phe Gly Ser His Phe Tyr Ser Phe Asn Gly Leu His Lys Tyr Lys
465 470 475 480
Lys Lys Phe Thr Pro Leu Trp Ser Glu Arg Tyr Ile Ser Cys Ser Arg
485 490 495
Ser Ser Trp Leu Ile Cys Ala Ile Cys Ala Leu Leu Met Glu Asp Ser
500 505 510
Lys Ile Lys Ile Val Lys
515

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<220>
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tca tta ttg gag aaa ata tct gtt gag cgt tct ttt att gaa ttt gat 96
Ser Leu Leu Glu Lys Ile Ser Val Glu Arg Ser Phe Ile Glu Phe Asp
20 25 30

aaa ctt cta tta gca cct tat tgg cgt aaa gga atg ctg gca cta ata 144
Lys Leu Leu Leu Ala Pro Tyr Trp Arg Lys Gly Met Leu Ala Leu Ile
35 40 45

gat agt cat gct ttt aat tat cta cca tgc tta aaa aat agg gaa tta 192
Asp Ser His Ala Phe Asn Tyr Leu Pro Cys Leu Lys Asn Arg Glu Leu
50 55 60

caa tta agc gcc ttt ttg tcc cag tta gat aaa gat ttt tta ttt gag 240
Gln Leu Ser Ala Phe Leu Ser Gln Leu Asp Lys Asp Phe Leu Phe Glu
65 70 75 80

aca tca gaa caa gct tgg gca tca ctc atc ttg agt atg gaa gtt gaa 288
Thr Ser Glu Gln Ala Trp Ala Ser Leu Ile Leu Ser Met Glu Val Glu
85 90 95

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cac aca aag act ttt tta aaa aaa tgg aag aca tca act cac ttt caa      336
His Thr Lys Thr Phe Leu Lys Lys Trp Lys Thr Ser Thr His Phe Gln
            100                 105                 110

aaa gat gtt gag cat ata gtg gat gtt tat cgt att cgt gaa caa atg      384
Lys Asp Val Glu His Ile Val Asp Val Tyr Arg Ile Arg Glu Gln Met
        115                 120                 125

gga ttg gct aaa gaa cat ctt tat cgt tat gga aaa act ata ata aaa      432
Gly Leu Ala Lys Glu His Leu Tyr Arg Tyr Gly Lys Thr Ile Ile Lys
    130                 135                 140

caa gcg gaa ggt att cgc aaa gca aga ggc ttg atg gtt gat ttc gaa      480
Gln Ala Glu Gly Ile Arg Lys Ala Arg Gly Leu Met Val Asp Phe Glu
145                 150                 155                 160

aaa ata gaa caa cta gat agt gag tta gca atc cat gat agg cat gag      528
Lys Ile Glu Gln Leu Asp Ser Glu Leu Ala Ile His Asp Arg His Glu
                165                 170                 175

ata gtt gtc aat ggt ggc acc tta atc aag aaa tta gga ata aaa cct      576
Ile Val Val Asn Gly Gly Thr Leu Ile Lys Lys Leu Gly Ile Lys Pro
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ggt cca cag atg gga gat att atc tct caa att gaa tta gcc att gtt      624
Gly Pro Gln Met Gly Asp Ile Ile Ser Gln Ile Glu Leu Ala Ile Val
        195                 200                 205

tta gga caa ctg att aat gaa gaa gag gct att tta cat ttt gtt aag      672
Leu Gly Gln Leu Ile Asn Glu Glu Glu Ala Ile Leu His Phe Val Lys
    210                 215                 220

cag tac ttg atg gat tagagaggat tat atg agc gat ttt tta gta gat       721
Gln Tyr Leu Met Asp                 Met Ser Asp Phe Leu Val Asp
225                                 230                 235

gga ttg act aag tcg gtt ggt gat aag acg gtc ttt agt aat gtt tca      769
Gly Leu Thr Lys Ser Val Gly Asp Lys Thr Val Phe Ser Asn Val Ser
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Phe Ile Ile His Ser Leu Asp Arg Ile Gly Ile Ile Gly Val Asn Gly
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act gga aag aca aca cta tta gat gtt att tcg ggt gaa tta ggt ttt      865
Thr Gly Lys Thr Thr Leu Leu Asp Val Ile Ser Gly Glu Leu Gly Phe
    270                 275                 280

gat ggt gat cgt tcc cct ttt tca tca gct aat gat tat aag att gct      913
Asp Gly Asp Arg Ser Pro Phe Ser Ser Ala Asn Asp Tyr Lys Ile Ala
285                 290                 295                 300

tat tta aaa caa gaa cca gac ttt gat gat tct cag aca att ttg gac      961
Tyr Leu Lys Gln Glu Pro Asp Phe Asp Asp Ser Gln Thr Ile Leu Asp
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acc gta ctt tct tct gac tta aga gag atg gct tta att aaa gaa tat
Thr Val Leu Ser Ser Asp Leu Arg Glu Met Ala Leu Ile Lys Glu Tyr     1009
            320                 325                 330

gaa tta ttg ctt aat cac tac gaa gaa agt aag caa tca cgt cta gag
Glu Leu Leu Leu Asn His Tyr Glu Glu Ser Lys Gln Ser Arg Leu Glu     1057
        335                 340                 345

aaa gta atg gca gaa atg gat tct tta gat gct tgg tct att gag agc
Lys Val Met Ala Glu Met Asp Ser Leu Asp Ala Trp Ser Ile Glu Ser     1105
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gaa gtc aaa aca gta tta tcc aaa tta ggt att act gat ttg cag ttg
Glu Val Lys Thr Val Leu Ser Lys Leu Gly Ile Thr Asp Leu Gln Leu     1153
365                 370                 375                 380

tcg gtt ggt gaa tta tca gga gga tta cga aga cgt gtt caa tta gcg
Ser Val Gly Glu Leu Ser Gly Gly Leu Arg Arg Arg Val Gln Leu Ala     1201
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Gln Val Leu Leu Asn Asp Ala Asp Leu Leu Leu Leu Asp Glu Pro Thr     1249
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aac cac tta gat att gac act att gca tgg tta acg aat ttt ttg aaa
Asn His Leu Asp Ile Asp Thr Ile Ala Trp Leu Thr Asn Phe Leu Lys     1297
        415                 420                 425

aat agt aaa aag aca gtg ctt ttt ata act cat gat cgt tat ttt cta
Asn Ser Lys Lys Thr Val Leu Phe Ile Thr His Asp Arg Tyr Phe Leu     1345
    430                 435                 440

gac aat gtt gca aca cgt att ttt gaa tta gat aag gca cag att aca
Asp Asn Val Ala Thr Arg Ile Phe Glu Leu Asp Lys Ala Gln Ile Thr     1393
445                 450                 455                 460

gaa tat caa ggc aat tat cag gat tat gtc cga ctt cgt gca gaa caa
Glu Tyr Gln Gly Asn Tyr Gln Asp Tyr Val Arg Leu Arg Ala Glu Gln     1441
                465                 470                 475

gac gag cgt gat gct gct agt tta cat aaa aag aaa cag ctt tat aaa
Asp Glu Arg Asp Ala Ala Ser Leu His Lys Lys Lys Gln Leu Tyr Lys     1489
            480                 485                 490

cag gaa cta gct tgg atg cgt act cag cca caa gct cgt gca acg aaa
Gln Glu Leu Ala Trp Met Arg Thr Gln Pro Gln Ala Arg Ala Thr Lys     1537
        495                 500                 505

caa cag gct cgt att aat cgt ttt caa aat cta aaa aac gat tta cac
Gln Gln Ala Arg Ile Asn Arg Phe Gln Asn Leu Lys Asn Asp Leu His     1585
    510                 515                 520

caa aca agc gat aca agc gat ttg gaa atg aca ttt gaa aca agt cga
Gln Thr Ser Asp Thr Ser Asp Leu Glu Met Thr Phe Glu Thr Ser Arg     1633
525                 530                 535                 540
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Ile Gly Lys Lys Val Ile Asn Phe Glu Asn Val Ser Phe Ser Tyr Pro
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Asp Lys Ser Ile Leu Lys Asp Phe Asn Leu Leu Ile Gln Asn Lys Asp
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cgt att ggc atc gtt gga gat aat ggt gtt gga aag tca acc tta ctt 1777
Arg Ile Gly Ile Val Gly Asp Asn Gly Val Gly Lys Ser Thr Leu Leu
575 580 585

aat tta att gtt caa gat tta cag ccg gat tcg ggt aat gtc tct att 1825
Asn Leu Ile Val Gln Asp Leu Gln Pro Asp Ser Gly Asn Val Ser Ile
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670 675 680

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685 690 695 700

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Thr Leu Thr Val Leu Glu Asn Phe Leu Gln Gly Phe Gly Gly Pro Val
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Ile Thr Val Ser His Asp Arg Tyr Phe Leu Asp Lys Val Ala Asn Lys
720 725 730

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735 740 745

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750 755 760

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aaa aga atg tct tac ttt gaa aaa caa gaa tgg gcg aca att gaa gac      2401
Lys Arg Met Ser Tyr Phe Glu Lys Gln Glu Trp Ala Thr Ile Glu Asp
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gat att atg ata ttg gaa aat act atc act cgt ata gaa aat gat atg      2449
Asp Ile Met Ile Leu Glu Asn Thr Ile Thr Arg Ile Glu Asn Asp Met
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Gln Thr Cys Gly Ser Asp Phe Thr Arg Leu Ser Asp Leu Gln Lys Glu
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845                 850                 855                 860

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tta gat aaa cct gat aca gca tat tca gac cct cac tta gat cat ttg      2691
Leu Asp Lys Pro Asp Thr Ala Tyr Ser Asp Pro His Leu Asp His Leu
        880                 885                 890

acc tca tac tac gaa aaa ata gag aag tca gga ttc ttt gtc att gag      2739
Thr Ser Tyr Tyr Glu Lys Ile Glu Lys Ser Gly Phe Phe Val Ile Glu
    895                 900                 905

gag aga gat gag att att ggc tgt ggc ggc ttt ggt ccg ctg aaa aat      2787
Glu Arg Asp Glu Ile Ile Gly Cys Gly Gly Phe Gly Pro Leu Lys Asn
910                 915                 920                 925

cta att gca gag atg cag aag gtg tac att gca gaa cgt ttc cgt ggt      2835
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Lys Gly Leu Ala Thr Asp Leu Val Lys Met Ile Glu Val Glu Ala Arg
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Lys Ile Gly Tyr Arg Gln Leu Tyr Leu Glu Thr Ala Ser Thr Leu Ser
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Arg Asn Asp Met Tyr Ala Lys Leu Gln Glu Tyr Ser His His Glu Tyr
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gaa cag ata ggt gta tct tca cta gtg aca cgt atg aca agc gat act      3465
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Val Arg Leu Arg Ala Glu Gln Asp Glu Arg Asp Ala Ala Ser Leu His
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Gly Cys Gly Gly Phe Gly Pro Leu Lys Asn Leu Ile Ala Glu Met Gln
65 70 75 80
Lys Val Tyr Ile Ala Glu Arg Phe Arg Gly Lys Gly Leu Ala Thr Asp
85 90 95
Leu Val Lys Met Ile Glu Val Glu Ala Arg Lys Ile Gly Tyr Arg Gln
100 105 110
Leu Tyr Leu Glu Thr Ala Ser Thr Leu Ser Arg Ala Thr Ala Val Tyr
115 120 125
Lys His Met Gly Tyr Cys Ala Leu Ser Gln Pro Ile Ala Asn Asp Gln
130 135 140
Gly His Thr Ala Met Asp Ile Trp Met Ile Lys Asp Leu
145 150 155

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<213> Streptococcus

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20 25 30

Pro Thr Ala Leu Ala Gly Met Ile Asp Asn Gly Val Thr Lys Gly Asp
35 40 45

Arg Thr Gly Val Tyr Leu Trp Thr Phe Ile Met Phe Ile Phe Val Val
50 55 60

Leu Gly Ile Ile Gly Arg Ile Thr Met Ala Tyr Ala Ser Ser Arg Leu
65 70 75 80

Thr Thr Thr Met Ile Arg Asp Met Arg Asn Asp Met Tyr Ala Lys Leu
85 90 95

Gln Glu Tyr Ser His His Glu Tyr Glu Gln Ile Gly Val Ser Ser Leu
100 105 110

Val Thr Arg Met Thr Ser Asp Thr Phe Val Leu Met Gln Phe Ala Glu
115 120 125

Met Ser Leu Arg Leu Gly Leu Val Thr Pro Met Val Met Ile Phe Ser
130 135 140

Val Val Met Ile Leu Ile Thr Ser Pro Ser Leu Ala Trp Leu Val Ala
145 150 155 160

Val Ala Met Pro Leu Leu Val Gly Val Val Leu Tyr Val Ala Ile Lys
165 170 175

Thr Lys Pro Leu Ser Glu Arg Gln Gln Thr Met Leu Asp Lys Ile Asn
180 185 190

Gln Tyr Val Arg Glu Asn Leu Thr Gly Leu Arg Val Val Arg Ala Phe
195 200 205

Ala Arg Glu Asn Phe Gln Ser Gln Lys Phe Gln Val Ala Asn Gln Arg
210 215 220

Tyr Thr Asp Thr Ser Thr Gly Leu Phe Lys Leu Thr Gly Leu Thr Glu
225 230 235 240

Pro Leu Phe Val Gln Ile Ile Ile Ala Met Ile Val Ala Ile Val Trp
245 250 255

Phe Ala Leu Asp Pro Leu Gln Arg Gly Ala Ile Lys Ile Gly Asp Leu
260 265 270

Val Ala Phe Ile Glu Tyr Ser Phe His Ala Leu Phe Ser Phe Leu Leu
275 280 285

Phe Ala Asn Leu Phe Thr Met Tyr Pro Arg Met Val Val Ser Ser His
290 295 300

Arg Ile Arg Glu Val Met Asp Met Pro Ile Ser Ile Asn Pro Asn Ala
305 310 315 320

Glu Gly Val Thr Asp Thr Lys Leu Lys Gly His Leu Glu Phe Asp Asn
325 330 335

Val Thr Phe Ala Tyr Pro Gly Glu Thr Glu Ser Pro Val Leu His Asp
340 345 350

Ile Ser Phe Lys Ala Lys Pro Gly Glu Thr Ile Ala Phe Ile Gly Ser
355 360 365

Thr Gly Ser Gly Lys Ser Ser Leu Val Asn Leu Ile Pro Arg Phe Tyr
370 375 380

Asp Val Thr Leu Gly Lys Ile Leu Val Asp Gly Val Asp Val Arg Asp
385 390 395 400

Tyr Asn Leu Lys Ser Leu Arg Gln Lys Ile Gly Phe Ile Pro Gln Lys
405 410 415

Ala Leu Leu Phe Thr Gly Thr Ile Gly Glu Asn Leu Lys Tyr Gly Lys
420 425 430

Ala Asp Ala Thr Ile Asp Asp Leu Arg Gln Ala Val Asp Ile Ser Gln
435 440 445
Ala Lys Glu Phe Ile Glu Ser His Gln Glu Ala Phe Glu Thr His Leu
450 455 460
Ala Glu Gly Gly Ser Asn Leu Ser Gly Gly Gln Lys Gln Arg Leu Ser
465 470 475 480
Ile Ala Arg Ala Val Val Lys Asp Pro Asp Leu Tyr Ile Phe Asp Asp
485 490 495
Ser Phe Ser Ala Leu Asp Tyr Lys Thr Asp Ala Thr Leu Arg Ala Arg
500 505 510
Leu Lys Glu Val Thr Gly Asp Ser Thr Val Leu Ile Val Ala Gln Arg
515 520 525
Val Gly Thr Ile Met Asp Ala Asp Gln Ile Ile Val Leu Asp Glu Gly
530 535 540
Glu Ile Val Gly Arg Gly Thr His Ala Gln Leu Ile Glu Asn Asn Ala
545 550 555 560
Ile Tyr Arg Glu Ile Ala Glu Ser Gln Leu Lys Asn Gln Asn Leu Ser
565 570 575
Glu Gly Glu

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Tyr Lys Ala Thr Leu Phe Leu Ala Ile Phe Leu Lys Val Leu Ser Ser
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Phe Met Ser Val Leu Glu Pro Phe Ile Leu Gly Leu Ala Ile Thr Glu
35 40 45
Leu Thr Ala Asn Leu Val Asp Met Ala Lys Gly Val Ser Gly Ala Glu
50 55 60
Leu Asn Val Pro Tyr Ile Ala Gly Ile Leu Ile Ile Tyr Phe Phe Arg
65 70 75 80
Gly Val Phe Tyr Glu Leu Gly Ser Tyr Gly Ser Asn
85 90

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Phe Gly Ser Ala Leu Ser Thr Val Glu Val Lys Glu Ile Ile Ser
1 5 10 15

gaa gaa aac ata tgg tta tat cgg ctc agt tgc tgc cat ttt act agc 95
Glu Glu Asn Ile Trp Leu Tyr Arg Leu Ser Cys Cys His Phe Thr Ser
20 25 30

tac tca tat tgg aag tta cca act tgg taagcatcat atg ggt cta gca 144
Tyr Ser Tyr Trp Lys Leu Pro Thr Trp Met Gly Leu Ala
35 40

aca aag gac aat cag att gcc tat att gat gac agc aaa ggt aag gca 192
Thr Lys Asp Asn Gln Ile Ala Tyr Ile Asp Asp Ser Lys Gly Lys Ala
45 50 55 60

aaa gcc cct aaa aca aac aaa acg atg gat caa atc agt gct gaa gaa 240
Lys Ala Pro Lys Thr Asn Lys Thr Met Asp Gln Ile Ser Ala Glu Glu
65 70 75

ggc atc tct gct gaa cag atc gta gtc aaa att act gac caa ggc tat 288
Gly Ile Ser Ala Glu Gln Ile Val Val Lys Ile Thr Asp Gln Gly Tyr
80 85 90

gtg acc tca cac ggt gac cat tat cat ttt tac aat ggg aaa gtt cct 336
Val Thr Ser His Gly Asp His Tyr His Phe Tyr Asn Gly Lys Val Pro
95 100 105

tat gat gcg att att agt gaa gag ttg ttg atg acg gat cct aat tac 384
Tyr Asp Ala Ile Ile Ser Glu Glu Leu Leu Met Thr Asp Pro Asn Tyr
110 115 120

cgt ttt aaa caa tca gac gtt atc aat gaa atc tta gac ggt tac gtt 432
Arg Phe Lys Gln Ser Asp Val Ile Asn Glu Ile Leu Asp Gly Tyr Val
125 130 135 140

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att aaa gtc aat ggc aac tat tat gtt tac ctc aag cca ggt agt aag     480
Ile Lys Val Asn Gly Asn Tyr Tyr Val Tyr Leu Lys Pro Gly Ser Lys
                145                 150                 155

cgc aaa aac att cga acc aaa caa caa att gct gag caa gta gcc aaa     528
Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile Ala Glu Gln Val Ala Lys
            160                 165                 170

gga act aaa gaa gct aaa gaa aaa ggt tta gct caa gtg gcc cat ctc     576
Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu Ala Gln Val Ala His Leu
        175                 180                 185

agt aaa gaa gaa gtt gcg gca gtc aat gaa gca aaa aga caa gga cgc     624
Ser Lys Glu Glu Val Ala Ala Val Asn Glu Ala Lys Arg Gln Gly Arg
    190                 195                 200

tat act aca gac gat ggc tat att ttt agt ccg aca gat atc att gat     672
Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser Pro Thr Asp Ile Ile Asp
205                 210                 215                 220

gat tta gga gat gct tat tta gta cct cat ggt aat cac tat cat tat     720
Asp Leu Gly Asp Ala Tyr Leu Val Pro His Gly Asn His Tyr His Tyr
                225                 230                 235

att cct aaa aag gat ttg tct cca agt gag cta gct gct gca caa gcc     768
Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu Leu Ala Ala Ala Gln Ala
            240                 245                 250

tac tgg agt caa aaa caa ggt cga ggt gct aga ccg tct gat tac cgc     816
Tyr Trp Ser Gln Lys Gln Gly Arg Gly Ala Arg Pro Ser Asp Tyr Arg
        255                 260                 265

ccg aca cca gcc cca ggt cgt agg aaa gcc cca att cct gat gtg acg     864
Pro Thr Pro Ala Pro Gly Arg Arg Lys Ala Pro Ile Pro Asp Val Thr
    270                 275                 280

cct aac cct gga caa ggt cat cag cca gat aac ggt ggc tat cat cca     912
Pro Asn Pro Gly Gln Gly His Gln Pro Asp Asn Gly Gly Tyr His Pro
285                 290                 295                 300

gcg cct cct agg cca aat gat gcg tca caa aac aaa cac caa aga gat     960
Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln Asn Lys His Gln Arg Asp
                305                 310                 315

gag ttt aaa gga aaa acc ttt aag gaa ctt tta gat caa cta cac cgt    1008
Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu Leu Asp Gln Leu His Arg
            320                 325                 330

ctt gat ttg aaa tac cgt cat gtg gaa gaa gat ggg ttg att ttt gaa    1056
Leu Asp Leu Lys Tyr Arg His Val Glu Glu Asp Gly Leu Ile Phe Glu
        335                 340                 345

ccg act caa gtg atc aaa tca aac gct ttt ggg tat gtg gtg cct cat    1104
Pro Thr Gln Val Ile Lys Ser Asn Ala Phe Gly Tyr Val Val Pro His
    350                 355                 360
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gga gat cat tat cat att atc cca aga agt cag tta tca cct ctt gaa 1152
Gly Asp His Tyr His Ile Ile Pro Arg Ser Gln Leu Ser Pro Leu Glu
365 370 375 380

atg gaa tta gca gat cga tac tta gct ggc caa act gag gac aat gac 1200
Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly Gln Thr Glu Asp Asn Asp
385 390 395

tca ggt tca gag cac tca aaa cca tca gat aaa gaa gtg aca cat acc 1248
Ser Gly Ser Glu His Ser Lys Pro Ser Asp Lys Glu Val Thr His Thr
400 405 410

ttt ctt ggt cat cgc atc aaa gct tac gga aaa ggc tta gat ggt aaa 1296
Phe Leu Gly His Arg Ile Lys Ala Tyr Gly Lys Gly Leu Asp Gly Lys
415 420 425

cca tat gat acg agt gat gct tat gtt ttt agt aaa gaa tcc att cat 1344
Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe Ser Lys Glu Ser Ile His
430 435 440

tca gtg gat aaa tca gga gtt aca gct aaa cac gga gat cat ttc cac 1392
Ser Val Asp Lys Ser Gly Val Thr Ala Lys His Gly Asp His Phe His
445 450 455 460

tat ata gga ttt gga gaa ctt gaa caa tat gag ttg gat gag gtc gct 1440
Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr Glu Leu Asp Glu Val Ala
465 470 475

aac tgg gtg aaa gca aaa ggt caa gct gat gag ctt gct gct gct ttg 1488
Asn Trp Val Lys Ala Lys Gly Gln Ala Asp Glu Leu Ala Ala Ala Leu
480 485 490

gat cag gaa caa ggc aaa gaa aaa cca ctc ttt gac act aaa aaa gtg 1536
Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu Phe Asp Thr Lys Lys Val
495 500 505

agt cgc aaa gta aca aaa gat ggt aaa gtg ggc tat atg atg cca aaa 1584
Ser Arg Lys Val Thr Lys Asp Gly Lys Val Gly Tyr Met Met Pro Lys
510 515 520

gat ggt aag gac tat ttc tat gct cgt gat caa ctt gat ttg act cag 1632
Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp Gln Leu Asp Leu Thr Gln
525 530 535 540

att gcc ttt gcc gaa caa gaa cta atg ctt aaa gat aag aag cat tac 1680
Ile Ala Phe Ala Glu Gln Glu Leu Met Leu Lys Asp Lys Lys His Tyr
545 550 555

cgt tat gac att gtt gac aca ggt att gag cca cga ctt gct gta gat 1728
Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu Pro Arg Leu Ala Val Asp
560 565 570

gtg tca agt ctg ccg atg cat gct ggt aat gct act tac gat act gga 1776
Val Ser Ser Leu Pro Met His Ala Gly Asn Ala Thr Tyr Asp Thr Gly
575 580 585

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agt tcg ttt gtt atc cca cat att gat cat atc cat gtc gtt ccg tat      1824
Ser Ser Phe Val Ile Pro His Ile Asp His Ile His Val Val Pro Tyr
    590                 595                 600

tca tgg ttg acg cgc gat cag att gca aca gtc aag tat gtg atg caa      1872
Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr Val Lys Tyr Val Met Gln
605                 610                 615                 620

cac ccc gaa gtt cgt ccg gat gta tgg tct aag cca ggg cat gaa gag      1920
His Pro Glu Val Arg Pro Asp Val Trp Ser Lys Pro Gly His Glu Glu
                625                 630                 635

tca ggt tcg gtc att cca aat gtt acg cct ctt gat aaa cgt gct ggt      1968
Ser Gly Ser Val Ile Pro Asn Val Thr Pro Leu Asp Lys Arg Ala Gly
            640                 645                 650

atg cca aac tgg caa att atc cat tct gct gaa gaa gtt caa aaa gcc      2016
Met Pro Asn Trp Gln Ile Ile His Ser Ala Glu Glu Val Gln Lys Ala
        655                 660                 665

cta gca gaa ggt cgt ttt gca aca cca gac ggc tat att ttc gat cca      2064
Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp Gly Tyr Ile Phe Asp Pro
    670                 675                 680

cga gat gtt ttg gcc aaa gaa act ttt gta tgg aaa gat ggc tcc ttt      2112
Arg Asp Val Leu Ala Lys Glu Thr Phe Val Trp Lys Asp Gly Ser Phe
685                 690                 695                 700

agc atc cca aga gca gat ggc agt tca ttg aga acc att aat aaa tct      2160
Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu Arg Thr Ile Asn Lys Ser
                705                 710                 715

gat cta tcc caa gct gag tgg caa caa gct caa gag tta ttg gca aag      2208
Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala Gln Glu Leu Leu Ala Lys
            720                 725                 730

aaa aat act ggt gat gct act gat acg gat aaa ccc aaa gaa aag caa      2256
Lys Asn Thr Gly Asp Ala Thr Asp Thr Asp Lys Pro Lys Glu Lys Gln
        735                 740                 745

cag gca gat aag agc aat gaa aac caa cag cca agt gaa gcc agt aaa      2304
Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln Pro Ser Glu Ala Ser Lys
    750                 755                 760

gaa gaa aaa gaa tca gat gac ttt ata gac agt tta cca gac tat ggt      2352
Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp Ser Leu Pro Asp Tyr Gly
765                 770                 775                 780

cta gat aga gca acc cta gaa gat cat atc aat caa tta gca caa aaa      2400
Leu Asp Arg Ala Thr Leu Glu Asp His Ile Asn Gln Leu Ala Gln Lys
                785                 790                 795

gct aat atc gat cct aag tat ctc att ttc caa cca gaa ggt gtc caa      2448
Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe Gln Pro Glu Gly Val Gln
            800                 805                 810
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ttt tat aat aaa aat ggt gaa ttg gta act tat gat atc aag aca ctt      2496
Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr Tyr Asp Ile Lys Thr Leu
        815                     820                     825

caa caa ata aac cct taaccaaaag aagatctcat tgttaaagca ctgctttgtc     2551
Gln Gln Ile Asn Pro
    830

aaagcaagtt acggtgattt tgaagtcatt ctatgtaacg agtagtgata aaagttggat  2611
aatagcggtt ttcttttgca aagaaatggt atccatgtta gaatagtaaa aaaagaggag  2671
gattcttgga ctaatgtcaa ataagtagac agaaaactgt gttattttattgcgt        2726
taaaataatt ttcttctttc tgattagggg ttagtcctag attagccgta tgtgggttgt  2786
aattgttata aaaattctca atgtattcaa agcagtctaa ttgaacctgt ttgatatttt  2846
gataatgttt tcggttgatt tgtctatgct ttaaatactt gaaaaatgct tcagttacgg  2906
cattatcata aggatatcca ggattagaaa aagaatgcat gatattggca ctgcacccta  2966
atagtgagac gcaagaaaaa cacttttaggcaatcagtt ttctgtactg tacaggcgac   3025
tggtcgttta atctctgttg aattctagtt tcattataaa atgtaatgta atttttaaca  3085
atatttgtta tactatcttt gttgtatttt ctcctattat ggaaataaaa ggtttcagtc  3145
tttaggacgg tgtgaaacca ttcaatacag gcattatctg caggtgttcc ttttcgagac  3205
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aagggtgtct agtacaaaat ccgtgtcctg acaatctgag atagtgtaag ctataatttc  3379
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gagctgttca attaattcaa taaggtcatc ttttttttgcg gcttctcata ctcctttttc  3739
caacggtaat aggtcgaccg cttgacctta aaacagtcta gaatgaaaac tatcgggtag  3799
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gcctcgatac tttttaaga ggtcaacctg taattgtaat tgttccactt cagacagatg   3917
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gttccttcaa tctttctttt attaagtgaa aaggcaacac ttttctgtac aacatttata  4337
aagtgttttt ctaggcaattaatc ttttagtcat tggtgtttgg tagttgagac        4391
taccatgaat gcggtggtaa ttccaccaat gaacatagtc tttagtctta agagctagtt  4451
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cggtcttgtg ccaaccaaga gacaggccga tgatttcacg gttgtatagg tcaatgatga  4751
ggcaaacata agcccaacga ttgcctacac gaacataggt taagtcagtg actaaggctt  4811
gtagtggtct ttcttgctta aattgcctgt ctaagtggtt gggaataggg gcttcattct  4871
tgcctctaga atgtggtttg aaggtggctt tctgataaac agaaaccaaa ttgagtcgct  4931
tcataatgcg tcgaatccga cgacgtgaaa gtgtgatacc ttcgttattc aagcatattt  4991
tgatttttct ggatccgtat ctagactcgc tatcgagaaa aattctttta atagtttctt  5051
caaactccgt ttcagatact gactccacgg cttgatagta ataacttgag tgtggcatat  5111
tcagccagcg acacatcttt gaaatgctgt atttatcctt attagcagtg attatttccc  5171
tttttgtgcc ataatcaccg ctgcttgctt taggatatct aatt                    5215
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<211> 40
<212> PRT

<213> Streptococcus

<400> 14

Phe Gly Ser Ala Leu Ser Thr Val Glu Val Lys Glu Ile Ile Ser Glu
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Glu Asn Ile Trp Leu Tyr Arg Leu Ser Cys Cys His Phe Thr Ser Tyr
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Ser Tyr Trp Lys Leu Pro Thr Trp
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<210> 15
<211> 793
<212> PRT
<213> Streptococcus

<400> 15

Met Gly Leu Ala Thr Lys Asp Asn Gln Ile Ala Tyr Ile Asp Asp Ser
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Lys Gly Lys Ala Lys Ala Pro Lys Thr Asn Lys Thr Met Asp Gln Ile
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Ser Ala Glu Glu Gly Ile Ser Ala Glu Gln Ile Val Val Lys Ile Thr
35 40 45
Asp Gln Gly Tyr Val Thr Ser His Gly Asp His Tyr His Phe Tyr Asn
50 55 60
Gly Lys Val Pro Tyr Asp Ala Ile Ile Ser Glu Glu Leu Leu Met Thr
65 70 75 80
Asp Pro Asn Tyr Arg Phe Lys Gln Ser Asp Val Ile Asn Glu Ile Leu
85 90 95
Asp Gly Tyr Val Ile Lys Val Asn Gly Asn Tyr Tyr Val Tyr Leu Lys
100 105 110
Pro Gly Ser Lys Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile Ala Glu
115 120 125
Gln Val Ala Lys Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu Ala Gln
130 135 140
Val Ala His Leu Ser Lys Glu Glu Val Ala Ala Val Asn Glu Ala Lys
145 150 155 160
Arg Gln Gly Arg Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser Pro Thr
165 170 175
Asp Ile Ile Asp Asp Leu Gly Asp Ala Tyr Leu Val Pro His Gly Asn
180 185 190
His Tyr His Tyr Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu Leu Ala
195 200 205
Ala Ala Gln Ala Tyr Trp Ser Gln Lys Gln Gly Arg Gly Ala Arg Pro
210 215 220
Ser Asp Tyr Arg Pro Thr Pro Ala Pro Gly Arg Arg Lys Ala Pro Ile
225 230 235 240
Pro Asp Val Thr Pro Asn Pro Gly Gln Gly His Gln Pro Asp Asn Gly
245 250 255
Gly Tyr His Pro Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln Asn Lys
260 265 270
His Gln Arg Asp Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu Leu Asp
275 280 285
Gln Leu His Arg Leu Asp Leu Lys Tyr Arg His Val Glu Glu Asp Gly
290 295 300
Leu Ile Phe Glu Pro Thr Gln Val Ile Lys Ser Asn Ala Phe Gly Tyr
305 310 315 320

Val Val Pro His Gly Asp His Tyr His Ile Ile Pro Arg Ser Gln Leu
325 330 335
Ser Pro Leu Glu Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly Gln Thr
340 345 350
Glu Asp Asn Asp Ser Gly Ser Glu His Ser Lys Pro Ser Asp Lys Glu
355 360 365
Val Thr His Thr Phe Leu Gly His Arg Ile Lys Ala Tyr Gly Lys Gly
370 375 380
Leu Asp Gly Lys Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe Ser Lys
385 390 395 400
Glu Ser Ile His Ser Val Asp Lys Ser Gly Val Thr Ala Lys His Gly
405 410 415
Asp His Phe His Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr Glu Leu
420 425 430
Asp Glu Val Ala Asn Trp Val Lys Ala Lys Gly Gln Ala Asp Glu Leu
435 440 445
Ala Ala Ala Leu Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu Phe Asp
450 455 460
Thr Lys Lys Val Ser Arg Lys Val Thr Lys Asp Gly Lys Val Gly Tyr
465 470 475 480
Met Met Pro Lys Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp Gln Leu
485 490 495
Asp Leu Thr Gln Ile Ala Phe Ala Glu Gln Glu Leu Met Leu Lys Asp
500 505 510
Lys Lys His Tyr Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu Pro Arg
515 520 525
Leu Ala Val Asp Val Ser Ser Leu Pro Met His Ala Gly Asn Ala Thr
530 535 540
Tyr Asp Thr Gly Ser Ser Phe Val Ile Pro His Ile Asp His Ile His
545 550 555 560
Val Val Pro Tyr Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr Val Lys
565 570 575
Tyr Val Met Gln His Pro Glu Val Arg Pro Asp Val Trp Ser Lys Pro
580 585 590
Gly His Glu Glu Ser Gly Ser Val Ile Pro Asn Val Thr Pro Leu Asp
595 600 605
Lys Arg Ala Gly Met Pro Asn Trp Gln Ile Ile His Ser Ala Glu Glu
610 615 620
Val Gln Lys Ala Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp Gly Tyr
625 630 635 640
Ile Phe Asp Pro Arg Asp Val Leu Ala Lys Glu Thr Phe Val Trp Lys
645 650 655
Asp Gly Ser Phe Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu Arg Thr
660 665 670
Ile Asn Lys Ser Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala Gln Glu
675 680 685
Leu Leu Ala Lys Lys Asn Thr Gly Asp Ala Thr Asp Thr Asp Lys Pro
690 695 700
Lys Glu Lys Gln Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln Pro Ser
705 710 715 720
Glu Ala Ser Lys Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp Ser Leu
725 730 735
Pro Asp Tyr Gly Leu Asp Arg Ala Thr Leu Glu Asp His Ile Asn Gln
740 745 750
Leu Ala Gln Lys Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe Gln Pro
755 760 765

Glu Gly Val Gln Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr Tyr Asp
    770   775   780
Ile Lys Thr Leu Gln Gln Ile Asn Pro
785   790

<210> 16
<211> 715
<212> PRT
<213> Streptococcus

<400> 16
Met Thr Asp Pro Asn Tyr Arg Phe Lys Gln Ser Asp Val Ile Asn Glu
 1   5   10   15
Ile Leu Asp Gly Tyr Val Ile Lys Val Asn Gly Asn Tyr Tyr Val Tyr
            20   25   30
Leu Lys Pro Gly Ser Lys Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile
        35   40   45
Ala Glu Gln Val Ala Lys Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu
    50   55   60
Ala Gln Val Ala His Leu Ser Lys Glu Glu Val Ala Ala Val Asn Glu
65   70   75   80
Ala Lys Arg Gln Gly Arg Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser
                85   90   95
Pro Thr Asp Ile Ile Asp Asp Leu Gly Asp Ala Tyr Leu Val Pro His
            100   105   110
Gly Asn His Tyr His Tyr Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu
        115   120   125
Leu Ala Ala Ala Gln Ala Tyr Trp Ser Gln Lys Gln Gly Arg Gly Ala
    130   135   140
Arg Pro Ser Asp Tyr Arg Pro Thr Pro Ala Pro Gly Arg Arg Lys Ala
145   150   155   160
Pro Ile Pro Asp Val Thr Pro Asn Pro Gly Gln Gly His Gln Pro Asp
                165   170   175
Asn Gly Gly Tyr His Pro Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln
            180   185   190
Asn Lys His Gln Arg Asp Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu
        195   200   205
Leu Asp Gln Leu His Arg Leu Asp Leu Lys Tyr Arg His Val Glu Glu
    210   215   220
Asp Gly Leu Ile Phe Glu Pro Thr Gln Val Ile Lys Ser Asn Ala Phe
225   230   235   240
Gly Tyr Val Val Pro His Gly Asp His Tyr His Ile Ile Pro Arg Ser
                245   250   255
Gln Leu Ser Pro Leu Glu Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly
            260   265   270
Gln Thr Glu Asp Asn Asp Ser Gly Ser Glu His Ser Lys Pro Ser Asp
        275   280   285
Lys Glu Val Thr His Thr Phe Leu Gly His Arg Ile Lys Ala Tyr Gly
    290   295   300
Lys Gly Leu Asp Gly Lys Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe
305   310   315   320
Ser Lys Glu Ser Ile His Ser Val Asp Lys Ser Gly Val Thr Ala Lys
                325   330   335
His Gly Asp His Phe His Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr
            340   345   350

Glu Leu Asp Glu Val Ala Asn Trp Val Lys Ala Lys Gly Gln Ala Asp
        355   360   365
Glu Leu Ala Ala Ala Leu Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu
    370   375   380
Phe Asp Thr Lys Lys Val Ser Arg Lys Val Thr Lys Asp Gly Lys Val
385   390   395   400
Gly Tyr Met Met Pro Lys Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp
                405   410   415
Gln Leu Asp Leu Thr Gln Ile Ala Phe Ala Glu Gln Glu Leu Met Leu
            420   425   430
Lys Asp Lys Lys His Tyr Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu
        435   440   445
Pro Arg Leu Ala Val Asp Val Ser Ser Leu Pro Met His Ala Gly Asn
    450   455   460
Ala Thr Tyr Asp Thr Gly Ser Ser Phe Val Ile Pro His Ile Asp His
465   470   475   480
Ile His Val Val Pro Tyr Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr
                485   490   495
Val Lys Tyr Val Met Gln His Pro Glu Val Arg Pro Asp Val Trp Ser
            500   505   510
Lys Pro Gly His Glu Glu Ser Gly Ser Val Ile Pro Asn Val Thr Pro
        515   520   525
Leu Asp Lys Arg Ala Gly Met Pro Asn Trp Gln Ile Ile His Ser Ala
    530   535   540
Glu Glu Val Gln Lys Ala Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp
545   550   555   560
Gly Tyr Ile Phe Asp Pro Arg Asp Val Leu Ala Lys Glu Thr Phe Val
                565   570   575
Trp Lys Asp Gly Ser Phe Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu
            580   585   590
Arg Thr Ile Asn Lys Ser Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala
        595   600   605
Gln Glu Leu Leu Ala Lys Lys Asn Thr Gly Asp Ala Thr Asp Thr Asp
    610   615   620
Lys Pro Lys Glu Lys Gln Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln
625   630   635   640
Pro Ser Glu Ala Ser Lys Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp
                645   650   655
Ser Leu Pro Asp Tyr Gly Leu Asp Arg Ala Thr Leu Glu Asp His Ile
            660   665   670
Asn Gln Leu Ala Gln Lys Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe
        675   680   685
Gln Pro Glu Gly Val Gln Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr
    690   695   700
Tyr Asp Ile Lys Thr Leu Gln Gln Ile Asn Pro
705   710   715

<210> 17
<211> 77
<212> PRT
<213> Streptococcus

<400> 17
Met His Ser Phe Ser Asn Pro Gly Tyr Pro Tyr Asp Asn Ala Val Thr
1   5   10   15

Glu Ala Phe Phe Lys Tyr Leu Lys His Arg Gln Ile Asn Arg Lys His
20 25 30
Tyr Gln Asn Ile Lys Gln Val Gln Leu Asp Cys Phe Glu Tyr Ile Glu
35 40 45
Asn Phe Tyr Asn Asn Tyr Asn Pro His Thr Ala Asn Leu Gly Leu Thr
50 55 60
Pro Asn Gln Lys Glu Glu Asn Tyr Phe Asn Ala Ile Lys
65 70 75

<210> 18
<211> 86
<212> PRT
<213> Streptococcus

<400> 18
Met Ala Tyr Tyr Gln Ala Cys Thr Glu Lys Asp Ile Ile Arg Ser Met
1 5 10 15
Ser Arg Lys Gly Thr Pro Ala Asp Asn Ala Cys Ile Glu Trp Phe His
20 25 30
Thr Val Leu Lys Thr Glu Thr Phe Tyr Phe His Asn Arg Arg Lys Tyr
35 40 45
Asn Lys Asp Ser Ile Thr Asn Ile Val Lys Asn Tyr Ile Thr Phe Tyr
50 55 60
Asn Glu Thr Arg Ile Gln Gln Arg Leu Asn Asp Gln Ser Pro Val Gln
65 70 75 80
Tyr Arg Lys Leu Ile Ala
85

<210> 19
<211> 126
<212> PRT
<213> Streptococcus

<400> 19
Met Glu Asn His Phe Ile Tyr Gly Tyr Arg Thr Ile Thr Arg Leu Leu
1 5 10 15
Lys Lys Ile His Gly Leu Thr Val Asn Thr Lys Lys Val Tyr Arg Ile
20 25 30
Met Lys Asn Asn Gly Trp Leu Cys Arg Thr Arg Thr Lys Lys Val Pro
35 40 45
Asn Leu Gly Lys Ala Tyr Tyr Leu Thr Asp Asn Lys Leu Ser Arg Asp
50 55 60
Phe His Ala Asp Lys Pro Lys Glu Lys Leu Val Thr Asp Ile Thr Tyr
65 70 75 80
Leu Tyr Phe Gly Asn Cys Lys Leu Tyr Leu Ser Ser Ile Met Asn Leu
85 90 95
Tyr Asn Arg Glu Ile Ile Ala Tyr Thr Ile Ser Asp Cys Gln Asp Thr
100 105 110
Asp Phe Val Leu Asp Thr Leu Asn Gln Leu Lys Leu Pro Lys
115 120 125

<210> 20
<211> 96
<212> PRT
<213> Streptococcus

<400> 20
Met Val Lys Lys Ala Tyr Ser Trp Glu Thr Lys Leu Ala Cys Ile Asp
1 5 10 15
Met Lys Lys Ala Gly Lys Ser Asn Arg Val Ile Met Glu Thr Leu Gly
20 25 30
Ile Lys Asn Asn Ser Gln Ile Tyr Thr Trp Met Lys Trp Tyr Glu Asn
35 40 45
Glu Glu Leu Tyr Arg Phe His Gln Gly Val Gly Lys Gln Tyr Thr Tyr
50 55 60
Gly Lys Gly Leu Glu His Leu Ser Glu Val Glu Gln Leu Gln Leu Gln
65 70 75 80
Val Asp Leu Leu Lys Lys Tyr Arg Gly Leu Ile Arg Lys Ser Ile Lys
85 90 95

<210> 21
<211> 288
<212> PRT
<213> streptococus

<400> 21
Ile Arg Tyr Pro Lys Ala Ser Ser Gly Asp Tyr Gly Thr Lys Arg Glu
1 5 10 15
Ile Ile Thr Ala Asn Lys Asp Lys Tyr Ser Ile Ser Lys Met Cys Arg
20 25 30
Trp Leu Asn Met Pro His Ser Ser Tyr Tyr Tyr Gln Ala Val Glu Ser
35 40 45
Val Ser Glu Thr Glu Phe Glu Glu Thr Ile Lys Arg Ile Phe Leu Asp
50 55 60
Ser Glu Ser Arg Tyr Gly Ser Arg Lys Ile Lys Ile Cys Leu Asn Asn
65 70 75 80
Glu Gly Ile Thr Leu Ser Arg Arg Arg Ile Arg Arg Ile Met Lys Arg
85 90 95
Leu Asn Leu Val Ser Val Tyr Gln Lys Ala Thr Phe Lys Pro His Ser
100 105 110
Arg Gly Lys Asn Glu Ala Pro Ile Pro Asn His Leu Asp Arg Gln Phe
115 120 125
Lys Gln Glu Arg Pro Leu Gln Ala Leu Val Thr Asp Leu Thr Tyr Val
130 135 140
Arg Val Gly Asn Arg Trp Ala Tyr Val Cys Leu Ile Ile Asp Leu Tyr
145 150 155 160
Asn Arg Glu Ile Ile Gly Leu Ser Leu Gly Trp His Lys Thr Ala Glu
165 170 175
Leu Val Lys Gln Ala Ile Gln Ser Ile Pro Tyr Ala Leu Thr Lys Val
180 185 190
Lys Met Phe His Ser Asp Arg Gly Lys Glu Phe Asp Asn Gln Leu Ile
195 200 205
Asp Glu Ile Leu Glu Ala Phe Gly Ile Thr Arg Ser Leu Ser Gln Ala
210 215 220
Gly Tyr Pro Tyr Asp Asn Ala Val Ala Glu Ser Thr Tyr Arg Ala Phe
225 230 235 240
Lys Ile Glu Phe Val Tyr Gln Glu Thr Phe Gln Leu Leu Glu Glu Leu
245 250 255
Ala Leu Lys Thr Lys Asp Tyr Val His Trp Trp Asn Tyr His Arg Ile
260 265 270
His Gly Ser Leu Asn Tyr Gln Thr Pro Met Thr Lys Arg Leu Ile Ala
275 280 285

<210> 22
<211> 5058
<212> DNA
<213> streptococcus

<220>
<221> CDS
<222> (1)...(663)

<221> CDS
<222> (763)...(1344)

<221> CDS
<222> (1362)...(1739)

<221> CDS
<222> (2266)...(5058)

<400> 22

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aat ttg aaa gca gaa tta tct gta gaa gat gag caa tat aca gca aca      48
Asn Leu Lys Ala Glu Leu Ser Val Glu Asp Glu Gln Tyr Thr Ala Thr
 1               5                  10                  15

gtt tat ggt aaa tct gct cat ggt tca aca cca caa gaa ggt gtt aat      96
Val Tyr Gly Lys Ser Ala His Gly Ser Thr Pro Gln Glu Gly Val Asn
            20                  25                  30

ggg gcg act tat tta gct ctt tat cta agt caa ttt gat ttt gaa ggt     144
Gly Ala Thr Tyr Leu Ala Leu Tyr Leu Ser Gln Phe Asp Phe Glu Gly
        35                  40                  45

cct gct cgt gct ttc tta gat gtt aca gcc aac att att cac gaa gac     192
Pro Ala Arg Ala Phe Leu Asp Val Thr Ala Asn Ile Ile His Glu Asp
    50                  55                  60

ttc tca ggt gaa aaa ctt gga gta gct tat gaa gat gac tgt atg gga     240
Phe Ser Gly Glu Lys Leu Gly Val Ala Tyr Glu Asp Asp Cys Met Gly
65                  70                  75                  80

cca ttg agc atg aat gca ggt gtc ttc cag ttt gat gaa act aat gat     288
Pro Leu Ser Met Asn Ala Gly Val Phe Gln Phe Asp Glu Thr Asn Asp
                85                  90                  95

gat aat act atc gct ctt aat ttc cgt tac cca caa ggg aca gat gct     336
Asp Asn Thr Ile Ala Leu Asn Phe Arg Tyr Pro Gln Gly Thr Asp Ala
            100                 105                 110

aaa act atc caa act aag ctt gag aaa ctt aac gga gtt gaa aaa gtg     384
Lys Thr Ile Gln Thr Lys Leu Glu Lys Leu Asn Gly Val Glu Lys Val
        115                 120                 125

act ctt tct gac cat gaa cac aca cca cac tat gta cct atg gac gat     432
Thr Leu Ser Asp His Glu His Thr Pro His Tyr Val Pro Met Asp Asp
    130                 135                 140
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gaa tta gta tca acc tta cta gct gtc tat gaa aag caa act ggt ctt     480
Glu Leu Val Ser Thr Leu Leu Ala Val Tyr Glu Lys Gln Thr Gly Leu
145                 150                 155                 160

aaa gga cat gaa cag gtt att ggt ggt ggg aca ttt ggt cgc tta ctt     528
Lys Gly His Glu Gln Val Ile Gly Gly Gly Thr Phe Gly Arg Leu Leu
                165                 170                 175

gaa cgg ggt gtt gca tac ggt gcc atg ttc cca gga gat gaa aac act     576
Glu Arg Gly Val Ala Tyr Gly Ala Met Phe Pro Gly Asp Glu Asn Thr
            180                 185                 190

atg cat caa gct aat gag tac atg cct tta gaa aat att ttc cgt tcg     624
Met His Gln Ala Asn Glu Tyr Met Pro Leu Glu Asn Ile Phe Arg Ser
        195                 200                 205

gct gct atc tac gca gaa gct atc tat gaa tta atc aaa taaaataatc     673
Ala Ala Ile Tyr Ala Glu Ala Ile Tyr Glu Leu Ile Lys
    210                 215                 220

cttaaactaa atatgtgatc aatgataaag ggtggtgaag acatgaaagt gtctttgcct  733
cttttcataa ggttagattt ggagacttt atg act gac ttg gaa aaa att att     786
                                Met Thr Asp Leu Glu Lys Ile Ile
                                            225

aaa gca ata aaa agt gat tca cag aat caa aat tat aca gaa aat ggt     834
Lys Ala Ile Lys Ser Asp Ser Gln Asn Gln Asn Tyr Thr Glu Asn Gly
230                 235                 240                 245

att gat cct ttg ttt gct gct cct aaa aca gct agg atc aat att gtt     882
Ile Asp Pro Leu Phe Ala Ala Pro Lys Thr Ala Arg Ile Asn Ile Val
                250                 255                 260

ggc caa gca cct ggt tta aaa act caa gaa gca aga ctc tat tgg aaa     930
Gly Gln Ala Pro Gly Leu Lys Thr Gln Glu Ala Arg Leu Tyr Trp Lys
            265                 270                 275

gat aaa tct gga gat cgt cta cgc cag tgg ctt gga gtt gat gaa gag     978
Asp Lys Ser Gly Asp Arg Leu Arg Gln Trp Leu Gly Val Asp Glu Glu
        280                 285                 290

aca ttt tac cat tct gga aaa ttt gct gtt tta cct tta gat ttt tat     1026
Thr Phe Tyr His Ser Gly Lys Phe Ala Val Leu Pro Leu Asp Phe Tyr
    295                 300                 305

tac cca ggc aaa gga aaa tca gga gat tta ccc cct aga aaa ggt ttt     1074
Tyr Pro Gly Lys Gly Lys Ser Gly Asp Leu Pro Pro Arg Lys Gly Phe
310                 315                 320                 325

gcg gag aaa tgg cac cct ctt att tta aaa gaa atg cct aat gtt caa     1122
Ala Glu Lys Trp His Pro Leu Ile Leu Lys Glu Met Pro Asn Val Gln
                330                 335                 340

ttg acc ttg cta gtt ggt cag tat gct cag aaa tat tat ctt gga agc     1170
Leu Thr Leu Leu Val Gly Gln Tyr Ala Gln Lys Tyr Tyr Leu Gly Ser
            345                 350                 355
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tcc gca cat aaa aat cta aca gaa aca gtt aaa gct tac aaa gac tat 1218
Ser Ala His Lys Asn Leu Thr Glu Thr Val Lys Ala Tyr Lys Asp Tyr
360 365 370

cta ccc gat tat tta ccc ctg gtt cac cca tca ccg cga aat caa att 1266
Leu Pro Asp Tyr Leu Pro Leu Val His Pro Ser Pro Arg Asn Gln Ile
375 380 385

tgg cta aag aag aat cca tgg ttt gaa aaa gat cta atc gtt gat tta 1314
Trp Leu Lys Lys Asn Pro Trp Phe Glu Lys Asp Leu Ile Val Asp Leu
390 395 400 405

caa aag ata gta gca gat att tta aaa gat taaggatagg agttggt atg 1364
Gln Lys Ile Val Ala Asp Ile Leu Lys Asp Met
410 415

aga gat aat cat cta cac acg tat ttt tcc tat gat tgt caa acg gca 1412
Arg Asp Asn His Leu His Thr Tyr Phe Ser Tyr Asp Cys Gln Thr Ala
420 425 430

ttt gag gac tat att aat ggt ttt aca ggt gaa ttt atc acg aca gaa 1460
Phe Glu Asp Tyr Ile Asn Gly Phe Thr Gly Glu Phe Ile Thr Thr Glu
435 440 445

cat ttt gat tta tca aat cct tac acc ggt caa gac gat gtt cct gat 1508
His Phe Asp Leu Ser Asn Pro Tyr Thr Gly Gln Asp Asp Val Pro Asp
450 455 460

tat agt gct tat tgt caa aaa ata gat tat ctt aat cag aaa tat gga 1556
Tyr Ser Ala Tyr Cys Gln Lys Ile Asp Tyr Leu Asn Gln Lys Tyr Gly
465 470 475 480

aat cga ttt aaa aaa gga att gaa atc ggt tat ttt aaa gat agg gaa 1604
Asn Arg Phe Lys Lys Gly Ile Glu Ile Gly Tyr Phe Lys Asp Arg Glu
485 490 495

tca gat att tta gat tat tta aaa aat aaa gaa ttt gat tta aaa cta 1652
Ser Asp Ile Leu Asp Tyr Leu Lys Asn Lys Glu Phe Asp Leu Lys Leu
500 505 510

ttg tca atc cat cat aat ggt agg tat gat tat ctg caa gaa gaa gct 1700
Leu Ser Ile His His Asn Gly Arg Tyr Asp Tyr Leu Gln Glu Glu Ala
515 520 525

ctg aaa gta cca aca aag gga gct ttt agc aga tta ctt taatcgtatg 1749
Leu Lys Val Pro Thr Lys Gly Ala Phe Ser Arg Leu Leu
530 535 540

gaatttgcca taggccgtgt ggaagcgcac gttttagctc actttgatta tggttttcgt 1809
aagttaaact tagatgtaga agatttaaaa ccgtttgaaa cgcaattgaa gcgcattttc 1869
ataaagatgt tatctaaggg gttagctttt gaactaaata ccaaatccct ttatctatat 1929
gggaatgaaa aactttatcg ctatgcttta gagatactca aacagcttgg ttgtaaacaa 1989
tactctatag gctctgacgg tcatattcct gaacattttt gttatgaatt tgatagactt 2049
caaggtctgc taaaggacta tcaaattgat gaaaatcatt tgatatgagg aaatttttga 2109
taaaaaagct aggcaatatt gcttagcttt tttgtaatgc tattgatagt tttagtgaaa 2169

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atttcaaaaa aataaagaaa tcatttactt gttgcaagcg cttgcgtaaa ttgttatgat 2229
tttattggta acaattcatt aaaaaaggag aatgat atg aaa aga aaa gac tta    2283
                                        Met Lys Arg Lys Asp Leu
                                                    545

ttt ggt gat aaa caa act caa tac acg att aga aag tta agt gtt gga    2331
Phe Gly Asp Lys Gln Thr Gln Tyr Thr Ile Arg Lys Leu Ser Val Gly
        550                 555                 560

gta gct tca gtt aca aca ggg gta tgt att ttt ctt cat agt cca cag    2379
Val Ala Ser Val Thr Thr Gly Val Cys Ile Phe Leu His Ser Pro Gln
    565                 570                 575

gta ttt gct gaa gaa gta agt gtt tct cct gca act aca gcg att gca    2427
Val Phe Ala Glu Glu Val Ser Val Ser Pro Ala Thr Thr Ala Ile Ala
580                 585                 590                 595

gag tcg aat att aat cag gtt gac aac caa caa tct act aat tta aaa    2475
Glu Ser Asn Ile Asn Gln Val Asp Asn Gln Gln Ser Thr Asn Leu Lys
                600                 605                 610

gat gac ata aac tca aac tct gag acg gtt gtg aca ccc tca gat atg    2523
Asp Asp Ile Asn Ser Asn Ser Glu Thr Val Val Thr Pro Ser Asp Met
            615                 620                 625

ccg gat acc aag caa tta gta tca gat gaa act gac act caa aag gga    2571
Pro Asp Thr Lys Gln Leu Val Ser Asp Glu Thr Asp Thr Gln Lys Gly
        630                 635                 640

gtg aca gag ccg gat aag gcg aca agc ctg ctt gaa gaa aat aaa ggt    2619
Val Thr Glu Pro Asp Lys Ala Thr Ser Leu Leu Glu Glu Asn Lys Gly
    645                 650                 655

cct gtt tca gat aaa aat acc tta gat tta aaa gta gca cca tct aca    2667
Pro Val Ser Asp Lys Asn Thr Leu Asp Leu Lys Val Ala Pro Ser Thr
660                 665                 670                 675

ttg caa aat act ccc gac aaa act tct caa gct ata ggt gct cca agc    2715
Leu Gln Asn Thr Pro Asp Lys Thr Ser Gln Ala Ile Gly Ala Pro Ser
                680                 685                 690

cct acc ttg aaa gta gct aat caa gct cca cgg att gaa aat ggt tac    2763
Pro Thr Leu Lys Val Ala Asn Gln Ala Pro Arg Ile Glu Asn Gly Tyr
            695                 700                 705

ttt agg cta cat ctt aaa gaa ttg cct caa ggt cat cct gta gaa agc    2811
Phe Arg Leu His Leu Lys Glu Leu Pro Gln Gly His Pro Val Glu Ser
        710                 715                 720

act gga ctt tgg ata tgg gga gat gtt gat caa ccg tct agt aat tgg    2859
Thr Gly Leu Trp Ile Trp Gly Asp Val Asp Gln Pro Ser Ser Asn Trp
    725                 730                 735

cca aat ggt gct atc cct atg act gat gct aag aaa gat gat tac ggt    2907
Pro Asn Gly Ala Ile Pro Met Thr Asp Ala Lys Lys Asp Asp Tyr Gly
740                 745                 750                 755
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tat tat gtt gat ttt aaa tta tct gaa aaa caa cga aaa caa ata tct
Tyr Tyr Val Asp Phe Lys Leu Ser Glu Lys Gln Arg Lys Gln Ile Ser 2955
760 765 770

ttt tta att aat aac aaa gca ggg aca aat tta agc ggc gat cat cat
Phe Leu Ile Asn Asn Lys Ala Gly Thr Asn Leu Ser Gly Asp His His 3003
775 780 785

att cca tta tta cga cct gag atg aac caa gtt tgg att gat gaa aag
Ile Pro Leu Leu Arg Pro Glu Met Asn Gln Val Trp Ile Asp Glu Lys 3051
790 795 800

tac ggt ata cat act tat caa ccc ctc aaa gaa ggg tat gtc cgt att
Tyr Gly Ile His Thr Tyr Gln Pro Leu Lys Glu Gly Tyr Val Arg Ile 3099
805 810 815

aac tat ttg agt tcc tct agt aac tat gac cac tta tca gca tgg ctc
Asn Tyr Leu Ser Ser Ser Ser Asn Tyr Asp His Leu Ser Ala Trp Leu 3147
820 825 830 835

ttt aaa gat gtt gca acc ccy tca aca act tgg cca gat ggt agt aat
Phe Lys Asp Val Ala Thr Xaa Ser Thr Thr Trp Pro Asp Gly Ser Asn 3195
840 845 850

ttt gtg aat caa gga cta tat gga agg tat att gat gta tca cta aaa
Phe Val Asn Gln Gly Leu Tyr Gly Arg Tyr Ile Asp Val Ser Leu Lys 3243
855 860 865

act aac gcc aaa gag att ggt ttt cta atc tta gat gaa agt aag aca
Thr Asn Ala Lys Glu Ile Gly Phe Leu Ile Leu Asp Glu Ser Lys Thr 3291
870 875 880

gga gat gca gtg aaa gtt caa ccc aac gac tat gtt ttt aga gat tta
Gly Asp Ala Val Lys Val Gln Pro Asn Asp Tyr Val Phe Arg Asp Leu 3339
885 890 895

gct aac cat aac caa att ttt gta aaa gat aag gat cca aag gtt tat
Ala Asn His Asn Gln Ile Phe Val Lys Asp Lys Asp Pro Lys Val Tyr 3387
900 905 910 915

aat aat cct tat tac att gat caa gtg cag cta aag gat gcc caa caa
Asn Asn Pro Tyr Tyr Ile Asp Gln Val Gln Leu Lys Asp Ala Gln Gln 3435
920 925 930

att gat tta aca agt att caa gca agt ttt aca act cta gat ggg gta
Ile Asp Leu Thr Ser Ile Gln Ala Ser Phe Thr Thr Leu Asp Gly Val 3483
935 940 945

gat aaa act gaa att tta aaa gaa ttg aaa gtg act gat aaa aat caa
Asp Lys Thr Glu Ile Leu Lys Glu Leu Lys Val Thr Asp Lys Asn Gln 3531
950 955 960

aat gct ata caa att tct gat atc act ctc gat act agt aaa tct ctt
Asn Ala Ile Gln Ile Ser Asp Ile Thr Leu Asp Thr Ser Lys Ser Leu 3579
965 970 975

tta ata atc aaa ggc gac ttt aat cct aaa caa ggt cat ttc aac ata 3627
Leu Ile Ile Lys Gly Asp Phe Asn Pro Lys Gln Gly His Phe Asn Ile
980 985 990 995

tct tat aat ggt aac aat gtc atg aca agg caa tct tgg gaa ttt aaa 3675
Ser Tyr Asn Gly Asn Asn Val Met Thr Arg Gln Ser Trp Glu Phe Lys
1000 1005 1010

gac caa ctt tat gct tat agt gga aat tta ggt gca gtt ctc aat caa 3723
Asp Gln Leu Tyr Ala Tyr Ser Gly Asn Leu Gly Ala Val Leu Asn Gln
1015 1020 1025

gat ggt tca aaa gtt gaa gcc agc ctc tgg tca ccg agt gct gat agt 3771
Asp Gly Ser Lys Val Glu Ala Ser Leu Trp Ser Pro Ser Ala Asp Ser
1030 1035 1040

gtc act atg att att tat gac aaa gat aac caa aac agg gtt gta gcg 3819
Val Thr Met Ile Ile Tyr Asp Lys Asp Asn Gln Asn Arg Val Val Ala
1045 1050 1055

act acc ccc ctt gtg aaa aat aat aaa ggt gtt tgg cag acg ata ctt 3867
Thr Thr Pro Leu Val Lys Asn Asn Lys Gly Val Trp Gln Thr Ile Leu
1060 1065 1070 1075

gat act aaa tta ggt att aaa aac tat act ggt tac tat tat ctt tac 3915
Asp Thr Lys Leu Gly Ile Lys Asn Tyr Thr Gly Tyr Tyr Tyr Leu Tyr
1080 1085 1090

gaa ata aaa aga ggt aag gat aag gtt aag att tta gat cct tat gca 3963
Glu Ile Lys Arg Gly Lys Asp Lys Val Lys Ile Leu Asp Pro Tyr Ala
1095 1100 1105

aag tca tta gca gag tgg gat agt aat act gtt aat gat gat att aaa 4011
Lys Ser Leu Ala Glu Trp Asp Ser Asn Thr Val Asn Asp Asp Ile Lys
1110 1115 1120

acg gct aaa gca gct ttt gta aat cca agt caa ctt gga cct caa aat 4059
Thr Ala Lys Ala Ala Phe Val Asn Pro Ser Gln Leu Gly Pro Gln Asn
1125 1130 1135

tta agt ttt gct aaa att gct aat ttt aaa gga aga caa gat gct gtt 4107
Leu Ser Phe Ala Lys Ile Ala Asn Phe Lys Gly Arg Gln Asp Ala Val
1140 1145 1150 1155

ata tac gaa gca cat gta aga gac ttc act tct gat cga tct ttg gat 4155
Ile Tyr Glu Ala His Val Arg Asp Phe Thr Ser Asp Arg Ser Leu Asp
1160 1165 1170

gga aaa tta aaa aat caa ttt ggt acc ttt gca gcc ttt tca gag aaa 4203
Gly Lys Leu Lys Asn Gln Phe Gly Thr Phe Ala Ala Phe Ser Glu Lys
1175 1180 1185

cta gat tat tta cag aaa tta gga gtt aca cac att cag ctt tta ccg 4251
Leu Asp Tyr Leu Gln Lys Leu Gly Val Thr His Ile Gln Leu Leu Pro
1190 1195 1200

gta ttg agt tat ttt tat gtt aat gaa atg gat aag tca cgc tca aca
Val Leu Ser Tyr Phe Tyr Val Asn Glu Met Asp Lys Ser Arg Ser Thr 4299
1205 1210 1215

gct tac act tcc tca gac aat aat tac aat tgg ggc tat gac cca cag
Ala Tyr Thr Ser Ser Asp Asn Asn Tyr Asn Trp Gly Tyr Asp Pro Gln 4347
1220 1225 1230 1235

agc tat ttt gct ctt tct ggg atg tat tca gag aaa cca aaa gat cca
Ser Tyr Phe Ala Leu Ser Gly Met Tyr Ser Glu Lys Pro Lys Asp Pro 4395
1240 1245 1250

tca gca cgt atc gcc gaa tta aaa caa tta ata cat gat att cat aaa
Ser Ala Arg Ile Ala Glu Leu Lys Gln Leu Ile His Asp Ile His Lys 4443
1255 1260 1265

cgt ggc atg ggg gtt ata ctt gat gtc gtc tat aat cac act gca aaa
Arg Gly Met Gly Val Ile Leu Asp Val Val Tyr Asn His Thr Ala Lys 4491
1270 1275 1280

act tat ctc ttt gag gat ata gaa cct aat tat tat cac ttt atg aat
Thr Tyr Leu Phe Glu Asp Ile Glu Pro Asn Tyr Tyr His Phe Met Asn 4539
1285 1290 1295

gaa gat ggt tca cca aga gaa agt ttt gga ggg gga cgt tta gga acc
Glu Asp Gly Ser Pro Arg Glu Ser Phe Gly Gly Gly Arg Leu Gly Thr 4587
1300 1305 1310 1315

act cat gca atg agt cgt cgt gtt ttg gtt gat tcc att aaa tat ctt
Thr His Ala Met Ser Arg Arg Val Leu Val Asp Ser Ile Lys Tyr Leu 4635
1320 1325 1330

aca agt gaa ttt aaa gtt gat ggt ttc cgt ttt gat atg atg gga gat
Thr Ser Glu Phe Lys Val Asp Gly Phe Arg Phe Asp Met Met Gly Asp 4683
1335 1340 1345

cat gat gcg gct gcg att gaa tta gct tat aaa gaa gct aaa gct att
His Asp Ala Ala Ala Ile Glu Leu Ala Tyr Lys Glu Ala Lys Ala Ile 4731
1350 1355 1360

aat cct aat atg att atg att ggt gag ggc tgg aga aca ttc caa ggc
Asn Pro Asn Met Ile Met Ile Gly Glu Gly Trp Arg Thr Phe Gln Gly 4779
1365 1370 1375

gat caa ggt cag ccg gtt aaa cca gct gac caa gat tgg atg aag tca
Asp Gln Gly Gln Pro Val Lys Pro Ala Asp Gln Asp Trp Met Lys Ser 4827
1380 1385 1390 1395

acc gat aca gtt ggc gtc ttt tca gat gat att cgt aat agc ttg aaa
Thr Asp Thr Val Gly Val Phe Ser Asp Asp Ile Arg Asn Ser Leu Lys 4875
1400 1405 1410

tct ggt ttt cca aat gaa ggt act cca gct ttc atc aca ggt ggc cca
Ser Gly Phe Pro Asn Glu Gly Thr Pro Ala Phe Ile Thr Gly Gly Pro 4923
1415 1420 1425

caa tct tta caa ggt att ttt aaa aat atc aaa gca caa cct ggg aat 4971
Gln Ser Leu Gln Gly Ile Phe Lys Asn Ile Lys Ala Gln Pro Gly Asn
1430 1435 1440

ttt gaa gca gat tcg cca gga gat gtg gtg cag tat att gct gca cat 5019
Phe Glu Ala Asp Ser Pro Gly Asp Val Val Gln Tyr Ile Ala Ala His
1445 1450 1455

gat aac ctt acc ttg cat gat gtg att gca aaa tca att 5058
Asp Asn Leu Thr Leu His Asp Val Ile Ala Lys Ser Ile
1460 1465 1470

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35 40 45
Pro Ala Arg Ala Phe Leu Asp Val Thr Ala Asn Ile Ile His Glu Asp
50 55 60
Phe Ser Gly Glu Lys Leu Gly Val Ala Tyr Glu Asp Asp Cys Met Gly
65 70 75 80
Pro Leu Ser Met Asn Ala Gly Val Phe Gln Phe Asp Glu Thr Asn Asp
85 90 95
Asp Asn Thr Ile Ala Leu Asn Phe Arg Tyr Pro Gln Gly Thr Asp Ala
100 105 110
Lys Thr Ile Gln Thr Lys Leu Glu Lys Leu Asn Gly Val Glu Lys Val
115 120 125
Thr Leu Ser Asp His Glu His Thr Pro His Tyr Val Pro Met Asp Asp
130 135 140
Glu Leu Val Ser Thr Leu Leu Ala Val Tyr Glu Lys Gln Thr Gly Leu
145 150 155 160
Lys Gly His Glu Gln Val Ile Gly Gly Gly Thr Phe Gly Arg Leu Leu
165 170 175
Glu Arg Gly Val Ala Tyr Gly Ala Met Phe Pro Gly Asp Glu Asn Thr
180 185 190
Met His Gln Ala Asn Glu Tyr Met Pro Leu Glu Asn Ile Phe Arg Ser
195 200 205
Ala Ala Ile Tyr Ala Glu Ala Ile Tyr Glu Leu Ile Lys
210 215 220

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<400> 24

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Lys Thr Ala Arg Ile Asn Ile Val Gly Gln Ala Pro Gly Leu Lys Thr
35 40 45
Gln Glu Ala Arg Leu Tyr Trp Lys Asp Lys Ser Gly Asp Arg Leu Arg
50 55 60
Gln Trp Leu Gly Val Asp Glu Glu Thr Phe Tyr His Ser Gly Lys Phe
65 70 75 80
Ala Val Leu Pro Leu Asp Phe Tyr Tyr Pro Gly Lys Gly Lys Ser Gly
85 90 95
Asp Leu Pro Pro Arg Lys Gly Phe Ala Glu Lys Trp His Pro Leu Ile
100 105 110
Leu Lys Glu Met Pro Asn Val Gln Leu Thr Leu Leu Val Gly Gln Tyr
115 120 125
Ala Gln Lys Tyr Tyr Leu Gly Ser Ser Ala His Lys Asn Leu Thr Glu
130 135 140
Thr Val Lys Ala Tyr Lys Asp Tyr Leu Pro Asp Tyr Leu Pro Leu Val
145 150 155 160
His Pro Ser Pro Arg Asn Gln Ile Trp Leu Lys Lys Asn Pro Trp Phe
165 170 175
Glu Lys Asp Leu Ile Val Asp Leu Gln Lys Ile Val Ala Asp Ile Leu
180 185 190
Lys Asp

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35 40 45
Asp Tyr Ser Ala Tyr Cys Gln Lys Ile Asp Tyr Leu Asn Gln Lys Tyr
50 55 60
Gly Asn Arg Phe Lys Lys Gly Ile Glu Ile Gly Tyr Phe Lys Asp Arg
65 70 75 80
Glu Ser Asp Ile Leu Asp Tyr Leu Lys Asn Lys Glu Phe Asp Leu Lys
85 90 95
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<400> 26

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Phe Leu His Ser Pro Gln Val Phe Ala Glu Glu Val Ser Val Ser Pro
35 40 45
Ala Thr Thr Ala Ile Ala Glu Ser Asn Ile Asn Gln Val Asp Asn Gln
50 55 60
Gln Ser Thr Asn Leu Lys Asp Asp Ile Asn Ser Asn Ser Glu Thr Val
65 70 75 80
Val Thr Pro Ser Asp Met Pro Asp Thr Lys Gln Leu Val Ser Asp Glu
85 90 95
Thr Asp Thr Gln Lys Gly Val Thr Glu Pro Asp Lys Ala Thr Ser Leu
100 105 110
Leu Glu Glu Asn Lys Gly Pro Val Ser Asp Lys Asn Thr Leu Asp Leu
115 120 125
Lys Val Ala Pro Ser Thr Leu Gln Asn Thr Pro Asp Lys Thr Ser Gln
130 135 140
Ala Ile Gly Ala Pro Ser Pro Thr Leu Lys Val Ala Asn Gln Ala Pro
145 150 155 160
Arg Ile Glu Asn Gly Tyr Phe Arg Leu His Leu Lys Glu Leu Pro Gln
165 170 175
Gly His Pro Val Glu Ser Thr Gly Leu Trp Ile Trp Gly Asp Val Asp
180 185 190
Gln Pro Ser Ser Asn Trp Pro Asn Gly Ala Ile Pro Met Thr Asp Ala
195 200 205
Lys Lys Asp Asp Tyr Gly Tyr Tyr Val Asp Phe Lys Leu Ser Glu Lys
210 215 220
Gln Arg Lys Gln Ile Ser Phe Leu Ile Asn Asn Lys Ala Gly Thr Asn
225 230 235 240
Leu Ser Gly Asp His His Ile Pro Leu Leu Arg Pro Glu Met Asn Gln
245 250 255
Val Trp Ile Asp Glu Lys Tyr Gly Ile His Thr Tyr Gln Pro Leu Lys
260 265 270
Glu Gly Tyr Val Arg Ile Asn Tyr Leu Ser Ser Ser Ser Asn Tyr Asp
275 280 285
His Leu Ser Ala Trp Leu Phe Lys Asp Val Ala Thr Xaa Ser Thr Thr
290 295 300
Trp Pro Asp Gly Ser Asn Phe Val Asn Gln Gly Leu Tyr Gly Arg Tyr
305 310 315 320
Ile Asp Val Ser Leu Lys Thr Asn Ala Lys Glu Ile Gly Phe Leu Ile
325 330 335
Leu Asp Glu Ser Lys Thr Gly Asp Ala Val Lys Val Gln Pro Asn Asp
340 345 350
Tyr Val Phe Arg Asp Leu Ala Asn His Asn Gln Ile Phe Val Lys Asp
355 360 365
Lys Asp Pro Lys Val Tyr Asn Asn Pro Tyr Tyr Ile Asp Gln Val Gln
370 375 380
Leu Lys Asp Ala Gln Gln Ile Asp Leu Thr Ser Ile Gln Ala Ser Phe
385 390 395 400
Thr Thr Leu Asp Gly Val Asp Lys Thr Glu Ile Leu Lys Glu Leu Lys
405 410 415
Val Thr Asp Lys Asn Gln Asn Ala Ile Gln Ile Ser Asp Ile Thr Leu
420 425 430
Asp Thr Ser Lys Ser Leu Leu Ile Ile Lys Gly Asp Phe Asn Pro Lys
435 440 445

Gln Gly His Phe Asn Ile Ser Tyr Asn Gly Asn Asn Val Met Thr Arg
450 455 460
Gln Ser Trp Glu Phe Lys Asp Gln Leu Tyr Ala Tyr Ser Gly Asn Leu
465 470 475 480
Gly Ala Val Leu Asn Gln Asp Gly Ser Lys Val Glu Ala Ser Leu Trp
485 490 495
Ser Pro Ser Ala Asp Ser Val Thr Met Ile Ile Tyr Asp Lys Asp Asn
500 505 510
Gln Asn Arg Val Val Ala Thr Thr Pro Leu Val Lys Asn Asn Lys Gly
515 520 525
Val Trp Gln Thr Ile Leu Asp Thr Lys Leu Gly Ile Lys Asn Tyr Thr
530 535 540
Gly Tyr Tyr Tyr Leu Tyr Glu Ile Lys Arg Gly Lys Asp Lys Val Lys
545 550 555 560
Ile Leu Asp Pro Tyr Ala Lys Ser Leu Ala Glu Trp Asp Ser Asn Thr
565 570 575
Val Asn Asp Asp Ile Lys Thr Ala Lys Ala Ala Phe Val Asn Pro Ser
580 585 590
Gln Leu Gly Pro Gln Asn Leu Ser Phe Ala Lys Ile Ala Asn Phe Lys
595 600 605
Gly Arg Gln Asp Ala Val Ile Tyr Glu Ala His Val Arg Asp Phe Thr
610 615 620
Ser Asp Arg Ser Leu Asp Gly Lys Leu Lys Asn Gln Phe Gly Thr Phe
625 630 635 640
Ala Ala Phe Ser Glu Lys Leu Asp Tyr Leu Gln Lys Leu Gly Val Thr
645 650 655
His Ile Gln Leu Leu Pro Val Leu Ser Tyr Phe Tyr Val Asn Glu Met
660 665 670
Asp Lys Ser Arg Ser Thr Ala Tyr Thr Ser Ser Asp Asn Asn Tyr Asn
675 680 685
Trp Gly Tyr Asp Pro Gln Ser Tyr Phe Ala Leu Ser Gly Met Tyr Ser
690 695 700
Glu Lys Pro Lys Asp Pro Ser Ala Arg Ile Ala Glu Leu Lys Gln Leu
705 710 715 720
Ile His Asp Ile His Lys Arg Gly Met Gly Val Ile Leu Asp Val Val
725 730 735
Tyr Asn His Thr Ala Lys Thr Tyr Leu Phe Glu Asp Ile Glu Pro Asn
740 745 750
Tyr Tyr His Phe Met Asn Glu Asp Gly Ser Pro Arg Glu Ser Phe Gly
755 760 765
Gly Gly Arg Leu Gly Thr Thr His Ala Met Ser Arg Arg Val Leu Val
770 775 780
Asp Ser Ile Lys Tyr Leu Thr Ser Glu Phe Lys Val Asp Gly Phe Arg
785 790 795 800
Phe Asp Met Met Gly Asp His Asp Ala Ala Ala Ile Glu Leu Ala Tyr
805 810 815
Lys Glu Ala Lys Ala Ile Asn Pro Asn Met Ile Met Ile Gly Glu Gly
820 825 830
Trp Arg Thr Phe Gln Gly Asp Gln Gly Gln Pro Val Lys Pro Ala Asp
835 840 845
Gln Asp Trp Met Lys Ser Thr Asp Thr Val Gly Val Phe Ser Asp Asp
850 855 860
Ile Arg Asn Ser Leu Lys Ser Gly Phe Pro Asn Glu Gly Thr Pro Ala
865 870 875 880
Phe Ile Thr Gly Gly Pro Gln Ser Leu Gln Gly Ile Phe Lys Asn Ile
885 890 895

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Lys Ala Gln Pro Gly Asn Phe Glu Ala Asp Ser Pro Gly Asp Val Val
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Lys Ser Ile
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    1               5                  10                  15

 cgt gct ggt gat act gta cgt gtt cac gct aaa gtt gtt gaa ggt act        97
 Arg Ala Gly Asp Thr Val Arg Val His Ala Lys Val Val Glu Gly Thr
             20                  25                  30

 cgc gaa cgt att cag atc ttt gaa ggt gtt gtt atc tca cgt aaa ggt       145
 Arg Glu Arg Ile Gln Ile Phe Glu Gly Val Val Ile Ser Arg Lys Gly
         35                  40                  45

 caa gga atc tca gaa atg tac aca gta cgt aaa att tct ggt ggt atc       193
 Gln Gly Ile Ser Glu Met Tyr Thr Val Arg Lys Ile Ser Gly Gly Ile
     50                  55                  60

 ggt gta gag cgt aca ttc cca att cac act cct cgt gtt gat aaa atc       241
 Gly Val Glu Arg Thr Phe Pro Ile His Thr Pro Arg Val Asp Lys Ile
 65                  70                  75                  80

 gaa gtt gtt cgt tat ggt aaa gta cgt cgt gct aaa ctt tac tac tta       289
 Glu Val Val Arg Tyr Gly Lys Val Arg Arg Ala Lys Leu Tyr Tyr Leu
                 85                  90                  95

 cgc gca ttg caa ggtaaagctg cacgtattaa agaaatccgt cgttaatttt           341
 Arg Ala Leu Gln
             100

 gatgatcaga ttttaaaaat gcttggttgt ttgaggatag taactatgtt ttaaaactgg     401
 acaaccaaga cgtaaaaaat ctgcctgtgg gcagtttttt tactaggtcc ccttagttca     461
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 ttggttgaaa tgataatccc aagttttatt aattgataaa tatttgttag tgtaatcaat     941
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<212> PRT
<213> streptococcus

<400> 28

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            20                  25                  30
Arg Glu Arg Ile Gln Ile Phe Glu Gly Val Val Ile Ser Arg Lys Gly
        35                  40                  45
Gln Gly Ile Ser Glu Met Tyr Thr Val Arg Lys Ile Ser Gly Gly Ile
    50                  55                  60
Gly Val Glu Arg Thr Phe Pro Ile His Thr Pro Arg Val Asp Lys Ile
65                  70                  75                  80
Glu Val Val Arg Tyr Gly Lys Val Arg Arg Ala Lys Leu Tyr Tyr Leu
                85                  90                  95
Arg Ala Leu Gln Gly Lys Ala Ala Arg Ile Lys Glu Ile Arg Arg
            100                 105                 110
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<211> 173
<212> PRT
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<400> 29

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            20                  25                  30
Gln Arg Tyr Leu Pro Thr Lys Asn Lys Ser Ser Ile Arg Asn Ile Pro
        35                  40                  45
Ile Asp Asn Asp Thr Leu Phe Phe Leu His Glu Phe Thr Lys Asn Lys
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    50                  55                  60
Asn Asp Arg Leu Phe Asp Lys Leu Ser Asn Asn Ala Val Asn Lys Thr
65                  70                  75                  80
Ile Arg Lys Ile Thr Gly Arg Glu Val Arg Val His Ser Leu Arg His
                85                  90                  95
Thr Phe Ala Ser Tyr Leu Ile Ser Ile Ser Gln Val Leu Asp His Glu
            100                 105                 110
Asn Leu Asn Ile Thr Leu Glu Val Tyr Ala His Gln Leu Gln Glu Gln
        115                 120                 125
Lys Asp Arg Asn Asp Lys Leu Asn Gln Arg Asn Leu Gly Gln Asn Ser
    130                 135                 140
Ser Lys Pro Leu Phe Thr Cys Asn Glu Tyr Val Pro Cys Arg Asn Arg
145                 150                 155                 160
Thr Ser Asn Tyr Ser Leu Gly Gly Ser Cys Tyr Ile His
                165                 170
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<211> 389
<212> PRT
<213> streptococcus

<400> 30

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            20                  25                  30
Gln Phe Lys Asn Ile Glu Lys Ile Lys Glu Val Glu Glu Lys Ile Phe
        35                  40                  45
Gln Tyr Asp Gly Leu Ala Lys Leu Lys Asp Leu Lys Val Val Ser Gly
    50                  55                  60
Glu Gln Ser Ile Asn Arg Glu Asp Leu Ser Asp Glu Phe Lys Asn Val
65                  70                  75                  80
Val Ser Leu Glu Ala Thr Ser Asn Thr Lys Arg Asn Leu Leu Phe Ser
                85                  90                  95
Ser Gly Val Phe Ser Phe Lys Glu Gly Lys Asn Ile Glu Glu Asn Asp
            100                 105                 110
Lys Asn Ser Ile Leu Val His Glu Glu Phe Ala Lys Gln Asn Lys Leu
        115                 120                 125
Lys Leu Gly Asp Glu Ile Asp Leu Glu Leu Leu Asp Thr Glu Lys Ser
    130                 135                 140
Gly Lys Ile Lys Ser His Lys Phe Lys Ile Ile Gly Ile Phe Ser Gly
145                 150                 155                 160
Lys Lys Gln Glu Thr Tyr Thr Gly Leu Ser Ser Asp Phe Ser Glu Asn
                165                 170                 175
Met Val Phe Val Asp Tyr Ser Thr Ser Gln Glu Ile Leu Asn Lys Ser
            180                 185                 190
Glu Asn Asn Arg Ile Ala Asn Lys Ile Leu Met Tyr Ser Gly Ser Leu
        195                 200                 205
Glu Ser Thr Glu Leu Ala Leu Asn Lys Leu Lys Asp Phe Lys Ile Asp
    210                 215                 220
Lys Ser Lys Tyr Ser Ile Lys Lys Asp Asn Lys Ala Phe Glu Glu Ser
225                 230                 235                 240
Leu Glu Ser Val Ser Gly Ile Lys His Ile Ile Lys Ile Met Thr Tyr
                245                 250                 255
Ser Ile Met Leu Gly Gly Ile Val Val Leu Ser Leu Ile Leu Ile Leu
            260                 265                 270
```

```
Trp Leu Arg Glu Arg Ile Tyr Glu Ile Gly Ile Phe Leu Ser Ile Gly
        275                 280                 285
Thr Thr Lys Ile Gln Ile Ile Arg Gln Phe Ile Phe Glu Leu Ile Phe
    290                 295                 300
Ile Ser Ile Pro Ser Ile Ile Ser Ser Leu Phe Leu Gly Asn Leu Leu
305                 310                 315                 320
Leu Lys Val Ile Val Glu Gly Phe Ile Asn Ser Glu Asn Ser Met Ile
                325                 330                 335
Phe Gly Gly Ser Leu Ile Asn Lys Ser Ser Phe Met Leu Asn Ile Thr
            340                 345                 350
Thr Leu Ala Glu Ser Tyr Leu Ile Leu Ile Ser Ile Ile Val Leu Ser
        355                 360                 365
Val Val Met Ala Ser Ser Leu Ile Leu Phe Lys Lys Pro Gln Glu Ile
    370                 375                 380
Leu Ser Lys Ile Ser
385
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<210> 31
<211> 169
<212> PRT
<213> streptococcus

<400> 31

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Met Asp Ile Leu Glu Ile Lys Asn Val Asn Tyr Ser Tyr Ala Asn Ser
1               5                   10                  15
Lys Glu Lys Val Leu Ser Gly Val Asn Gln Lys Phe Glu Leu Gly Lys
            20                  25                  30
Phe Tyr Ala Ile Val Gly Lys Ser Gly Thr Gly Lys Ser Thr Leu Leu
        35                  40                  45
Ser Leu Leu Ala Gly Leu Asp Lys Val Gln Thr Gly Lys Ile Leu Phe
    50                  55                  60
Lys Asn Glu Asp Ile Glu Lys Lys Gly Tyr Ser Asn His Arg Lys Asn
65                  70                  75                  80
Asn Ile Ser Leu Val Phe Gln Asn Tyr Asn Leu Ile Asp Tyr Leu Ser
                85                  90                  95
Pro Ile Glu Asn Ile Arg Leu Val Asn Lys Ser Val Asp Glu Ser Ile
            100                 105                 110
Leu Phe Glu Leu Gly Leu Asp Lys Lys Gln Ile Lys Arg Asn Val Met
        115                 120                 125
Lys Leu Ser Gly Gly Gln Gln Gln Arg Val Ala Ile Ala Arg Ala Leu
    130                 135                 140
Val Ser Asp Ala Pro Ile Ile Leu Ala Asp Glu Pro Thr Gly Asn Leu
145                 150                 155                 160
Asp Ser Val Thr Ala Gly Glu Ile Ile
                165
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<210> 32
<211> 4171
<212> DNA
<213> Streptococcus

<400> 32

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ttttcaatgg gaagtctctg gccactttca atactaacca attgattcgc gaagttgtct    180
atgttgaaat atccttagat actatgtcta gtggtgaaca tgatttagta aaagttaaca    240
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ttatcagacc cactaccgag catactatcc ccacgatgat gacagctagc ccctatcatc   300
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ttaaacagcc taaacacata caagttgaca caaaaccatt taaagaagaa gtaaaacatc   420
cttcaaaatt acccatcagc cctgcaactg aaagcttcac acacattgac agttatagtc   480
tcaatgacta ttttcttttct cgtggttttg ctaatatata cgtttcaggt gtgggtactg   540
ctggctctac gggtttcatg accagtgggg attaccaaca aatacaaagc tttaaagcag   600
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tcaaggctga ttggtcaaac ggccttgtag caaccacagg taaatcttat ctcggtacca   720
tgtcaactgg tttagcaaca actggcgttg aggggctgaa agtcattatc gctgaagccg   780
caatctccac atggtatgat tattatcgag aaaatgggct tgtgtgtagt ccaggcggct   840
accccggtga agatttagac gttttaacag aattaacata ctcacgaaac ctcttagctg   900
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caagacatgt ctacaaagtt ttcaatgcat tgcctcaaac catcaaaaaa cacctttttt  1140
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```

<210> 33
<211> 649
<212> PRT
<213> Streptococus

<400> 33

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Tyr Asp Asn Ile Phe Gln Ser Leu His His Leu Leu Ala Cys Arg Gly
1               5                   10                  15
Lys Ser Gly Asn Thr Leu Ile Asp Gln Leu Val Ala Asp Gly Leu Leu
            20                  25                  30
His Ala Asp Asn His Tyr His Phe Phe Asn Gly Lys Ser Leu Ala Thr
        35                  40                  45
Phe Asn Thr Asn Gln Leu Ile Arg Glu Val Val Tyr Val Glu Ile Ser
    50                  55                  60
Leu Asp Thr Met Ser Ser Gly Glu His Asp Leu Val Lys Val Asn Ile
65                  70                  75                  80
Ile Arg Pro Thr Thr Glu His Thr Ile Pro Thr Met Met Thr Ala Ser
                85                  90                  95
Pro Tyr His Gln Gly Ile Asn Asp Pro Ala Ala Asp Gln Lys Thr Tyr
            100                 105                 110
Gln Met Glu Gly Ala Leu Ala Val Lys Gln Pro Lys His Ile Gln Val
        115                 120                 125
Asp Thr Lys Pro Phe Lys Glu Glu Val Lys His Pro Ser Lys Leu Pro
    130                 135                 140
Ile Ser Pro Ala Thr Glu Ser Phe Thr His Ile Asp Ser Tyr Ser Leu
145                 150                 155                 160
Asn Asp Tyr Phe Leu Ser Arg Gly Phe Ala Asn Ile Tyr Val Ser Gly
                165                 170                 175
Val Gly Thr Ala Gly Ser Thr Gly Phe Met Thr Ser Gly Asp Tyr Gln
            180                 185                 190
Gln Ile Gln Ser Phe Lys Ala Val Ile Asp Trp Leu Asn Gly Lys Val
        195                 200                 205
Thr Ala Phe Thr Ser His Lys Arg Asp Lys Gln Val Lys Ala Asp Trp
    210                 215                 220
Ser Asn Gly Leu Val Ala Thr Thr Gly Lys Ser Tyr Leu Gly Thr Met
225                 230                 235                 240
Ser Thr Gly Leu Ala Thr Thr Gly Val Glu Gly Leu Lys Val Ile Ile
                245                 250                 255
Ala Glu Ala Ala Ile Ser Thr Trp Tyr Asp Tyr Tyr Arg Glu Asn Gly
            260                 265                 270
Leu Val Cys Ser Pro Gly Gly Tyr Pro Gly Glu Asp Leu Asp Val Leu
        275                 280                 285
Thr Glu Leu Thr Tyr Ser Arg Asn Leu Leu Ala Gly Asp Tyr Ile Lys
    290                 295                 300
Asn Asn Asp Cys Tyr Gln Ala Leu Leu Asn Glu Gln Ser Lys Ala Ile
```

```
305                 310                 315                 320
Asp Arg Gln Ser Gly Asp Tyr Asn Gln Tyr Trp His Asp Arg Asn Tyr
                325                 330                 335
Leu Thr His Val Asn Asn Val Lys Ser Arg Val Val Tyr Thr His Gly
            340                 345                 350
Leu Gln Asp Trp Asn Val Lys Pro Arg His Val Tyr Lys Val Phe Asn
        355                 360                 365
Ala Leu Pro Gln Thr Ile Lys Lys His Leu Phe Leu His Gln Gly Gln
    370                 375                 380
His Val Tyr Met His Asn Trp Gln Ser Ile Asp Phe Arg Glu Ser Met
385                 390                 395                 400
Asn Ala Leu Leu Ser Gln Glu Leu Leu Gly Ile Asp Asn His Phe Gln
                405                 410                 415
Leu Glu Glu Val Ile Trp Gln Asp Asn Thr Thr Glu Gln Thr Trp Gln
            420                 425                 430
Val Leu Asp Ala Phe Gly Gly Asn His Gln Glu Gln Ile Gly Leu Gly
        435                 440                 445
Asp Ser Lys Lys Leu Ile Asp Asn His Tyr Asp Lys Glu Ala Phe Asp
    450                 455                 460
Thr Tyr Cys Lys Asp Phe Asn Val Phe Lys Asn Asp Leu Phe Lys Gly
465                 470                 475                 480
Asn Asn Lys Thr Asn Gln Ile Thr Ile Asn Leu Pro Leu Lys Lys Asn
                485                 490                 495
Tyr Leu Leu Asn Gly Gln Cys Lys Leu His Leu Arg Val Lys Thr Ser
            500                 505                 510
Asp Lys Lys Ala Ile Leu Ser Ala Gln Ile Leu Asp Tyr Gly Pro Lys
        515                 520                 525
Lys Arg Phe Lys Asp Thr Pro Thr Ile Lys Phe Leu Asn Ser Leu Asp
    530                 535                 540
Asn Gly Lys Asn Phe Ala Arg Glu Ala Leu Arg Glu Leu Pro Phe Thr
545                 550                 555                 560
Lys Asp His Tyr Arg Val Ile Ser Lys Gly Val Leu Asn Leu Gln Asn
                565                 570                 575
Arg Thr Asp Leu Leu Thr Ile Glu Ala Ile Glu Pro Glu Gln Trp Phe
            580                 585                 590
Asp Ile Glu Phe Ser Leu Gln Pro Ser Ile Tyr Gln Leu Ser Lys Gly
        595                 600                 605
Asp Asn Leu Arg Ile Ile Leu Tyr Thr Thr Asp Phe Glu His Thr Ile
    610                 615                 620
Arg Asp Asn Ala Ser Tyr Ser Ile Thr Val Asp Leu Ser Gln Ser Tyr
625                 630                 635                 640
Leu Thr Ile Pro Thr Asn Gln Gly Asn
                645
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<210> 34
<211> 119
<212> PRT
<213> Streptococus

<400> 34

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Met Lys Leu Leu Thr Lys Glu Arg Phe Asp Asp Ser Gln His Phe Trp
1               5                   10                  15
Tyr Gln Ile Asn Leu Leu Gln Glu Ser Asn Phe Gly Ala Val Phe Asp
            20                  25                  30
His Asp Asn Lys Asn Ile Pro Gln Val Val Ala Thr Ile Val Asp Asp
        35                  40                  45
```

Leu Gln Gly Ser Gly Ser Ser Asn His Phe Trp Tyr Phe Gly Asn Thr
50 55 60
Thr Asp Thr Ser Ile Leu Met Ile Ala His Leu Asn Arg Lys Phe Tyr
65 70 75 80
Ile Gln Val Asn Leu Lys Asp Phe Asp Phe Ala Leu Asn Leu Ile Ala
85 90 95
Ile Asn Asn Trp Lys Ser Leu Leu Gln Thr Gln Leu Glu Ala Leu Asn
100 105 110
Asp Thr Leu Ala Ile Phe Gln
115

<210> 35
<211> 326
<212> PRT
<213> Streptococus

<400> 35
Met Ser Ser Tyr Trp Asn Asn Tyr Pro Glu Leu Lys Lys Asn Ile Asp
1 5 10 15
Glu Thr Asn Gln Leu Ile Gln Glu Arg Ile Gln Val Arg Asn Lys Asp
20 25 30
Ile Glu Ala Ala Leu Ser Gln Leu Thr Ala Ala Gly Gly Lys Gln Leu
35 40 45
Arg Pro Ala Phe Phe Tyr Leu Phe Ser Gln Leu Gly Asn Lys Glu Asn
50 55 60
Gln Asp Thr Gln Gln Leu Lys Lys Ile Ala Ala Ser Leu Glu Ile Leu
65 70 75 80
His Val Ala Thr Leu Ile His Asp Asp Val Ile Asp Asp Ser Pro Leu
85 90 95
Arg Arg Gly Asn Met Thr Ile Gln Ser Lys Phe Gly Lys Asp Ile Ala
100 105 110
Val Tyr Thr Gly Asp Leu Leu Phe Thr Val Phe Phe Asp Leu Ile Leu
115 120 125
Glu Ser Met Thr Asp Thr Pro Phe Met Arg Ile Asn Ala Lys Ser Met
130 135 140
Arg Lys Ile Leu Met Gly Glu Leu Asp Gln Met His Leu Arg Tyr Asn
145 150 155 160
Gln Gln Gln Gly Ile His His Tyr Leu Arg Ala Ile Ser Gly Lys Thr
165 170 175
Ala Glu Leu Phe Lys Leu Ala Ser Lys Glu Gly Ala Tyr Phe Gly Gly
180 185 190
Ala Glu Lys Glu Val Val Arg Leu Ala Gly His Ile Gly Phe Asn Ile
195 200 205
Gly Met Thr Phe Gln Ile Leu Asp Asp Ile Leu Asp Tyr Thr Ala Asp
210 215 220
Lys Lys Thr Phe Asn Lys Pro Val Leu Glu Asp Leu Thr Gln Gly Val
225 230 235 240
Tyr Ser Leu Pro Leu Leu Leu Ala Ile Glu Glu Asn Pro Asp Ile Phe
245 250 255
Lys Pro Ile Leu Asp Lys Lys Thr Asp Met Ala Thr Glu Asp Met Glu
260 265 270
Lys Ile Ala Tyr Leu Val Val Ser His Arg Gly Val Asp Lys Ala Arg
275 280 285
His Leu Ala Arg Lys Phe Thr Glu Lys Ala Ile Ser Asp Ile Asn Lys
290 295 300
Leu Pro Gln Asn Ser Ala Lys Lys Gln Leu Leu Gln Leu Thr Asn Tyr

```
305                 310                 315                 320
Leu Leu Lys Arg Lys Ile
                325

    <210> 36
    <211> 247
    <212> PRT
    <213> Streptococus

    <400> 36
Leu Pro Asn Lys Pro Tyr Asp Phe Ser Val Lys Asn Leu Ser Phe Gln
1               5                   10                  15
Tyr Lys Pro Gln Glu Lys Trp Val Leu His His Leu Asp Leu Asp Ile
            20                  25                  30
Lys Glu Gly Glu Lys Ile Ala Ile Leu Gly Arg Ser Gly Ser Gly Lys
        35                  40                  45
Ser Thr Leu Ala Ser Leu Leu Arg Gly Asp Leu Lys Ala Ser Gln Gly
    50                  55                  60
Lys Ile Thr Leu Gly Gly Ala Asp Val Ser Ile Val Gly Asp Cys Ile
65                  70                  75                  80
Ser Asn Tyr Ile Gly Val Ile Gln Gln Ala Pro Tyr Leu Phe Asn Thr
                85                  90                  95
Thr Leu Leu Asn Asn Ile Arg Ile Gly Asn Gln Asp Ala Ser Glu Glu
            100                 105                 110
Asp Val Trp Lys Val Leu Glu Arg Val Gly Leu Lys Glu Met Val Thr
        115                 120                 125
Asp Leu Ser Asp Gly Leu Tyr Thr Met Val Asp Glu Ala Gly Leu Arg
    130                 135                 140
Phe Ser Gly Gly Glu Arg His Arg Ile Ala Leu Ala Arg Ile Leu Leu
145                 150                 155                 160
Lys Asp Val Pro Ile Val Ile Leu Asp Glu Pro Thr Val Gly Leu Asp
                165                 170                 175
Pro Ile Thr Glu Gln Ala Leu Leu Arg Val Phe Met Lys Glu Leu Glu
            180                 185                 190
Gly Lys Thr Leu Val Trp Ile Thr His His Leu Lys Gly Ile Glu His
        195                 200                 205
Ala Asp Arg Ile Leu Phe Ile Glu Asn Gly Gln Leu Glu Leu Glu Gly
    210                 215                 220
Ser Pro Gln Glu Leu Ser Gln Ser Ser Gln Arg Tyr Arg Gln Leu Lys
225                 230                 235                 240
Ala Ala Asp Asp Gly Asp Leu
                245

    <210> 37
    <211> 3480
    <212> DNA
    <213> Streptococcus

    <400> 37
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ggagctggag ccaacttttc ttggatgaca gacttagcag gaaattgtgt catgattcaa    300
catgcggatg gaatgcatag tggttacgct catatgtcac gtgtggtggc taggactggg    360
gaaaaagtca aacaaggaga tatcatcggt tacgtaggag caactggtat ggcgacggga    420
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tcagctccaa gcattaagcc attacaatca gctcctgtac agaatcaatc tagtaaatta   600
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(11) International Publication Number: WO 99/42588

(43) International Publication Date: 26 August 1999 (26.08.99)

(21) International Application Number: PCT/CA99/00114

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60/075,425 20 February 1998 (20.02.98) US

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(74) Agents: CÔTE, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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(54) Title: GROUP B STREPTOCOCCUS ANTIGENS

(57) Abstract

Group B streptococcus (GBS) proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.

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MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
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RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

Interr ...al Application No
PCT/CA 99/00114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/31 C07K14/315 A61K39/09 C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MICHEL J L ET AL: "Cloned alpha and beta C-protein antigens of group B Streptococci elicit protective immunity" INFECTION AND IMMUNITY., vol. 59, no. 6, June 1991 (1991-06), pages 2023-2028, XP002107260 AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON., US ISSN: 0019-9567 the whole document ---	1-48

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1999	24 01 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lejeune, R

3

International Application No
PCT/CA 99/00114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LACHENAUER C S ET AL: "Cloning and expression in Escherichia coli of a protective surface protein from type V group B Streptococci" ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, vol. 418, 9 December 1997 (1997-12-09), pages 615-618, XP002107261 SPRING ST., NY, US ISSN: 0065-2598 the whole document ---	1-48
P,X	DATABASE EMBL [Online] Accession number AF062533, 11 February 1999 (1999-02-11) SPELLERBERG B ET AL: "Streptococcus agalactiae Lmb (lmb) gene, complete cds; and unknown gene." XP002125180 98.9% identity between base 1-2514 of SEQ ID NO 13 and base 988-3501 of AF062533 Translation product (AC: Q9ZHG9) has 98.5% identity in 793 AA overlap with SEQ ID NO 15 and 98.5% identity in 715 AA overlap with SEQ ID 16 & SPELLERBERG B ET AL: "Lmb, a protein with similarities to the LraI adhesin family, mediates attachment of Streptococcus agalactiae to human laminin" INFECTION AND IMMUNITY., vol. 67, no. 2, February 1999 (1999-02), pages 871-878, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON., US ISSN: 0019-9567 ---	1-10, 16-23,26
X	DATABASE EMBL [Online] Accession Number L23843, 4 January 1994 (1994-01-04) MACRINA F L ET AL: "ISN IS199 from Streptococcus mutans IS3 (Brathall serotype C) DNA fragment" XP002125181 79.6% identity between base 5212-4314 of SEQ ID NO 13 and base 312-1220 of L23843 Translation has 83.4% identity in 283 AA overlap with SEQ ID NO 21 --- -/--	1,3-7,10

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] Accession Number AF026542, 15 October 1997 (1997-10-15) HYNES W L ET AL: "Streptococcus pyogenes FF22 lantibiotic (scn) gene cluster region containing: scnK, scnR, streptococcin A-FF22 precursor (scnA), scnA1, scnM, scnT, scnF, scnE, scnG genes, complete cds, and tnpA gene, partial cds." XP002125182 88.2% identity between base 2607-2953 of SEQ ID NO 13 and base 10435-10777 of AF026542 Translation product (AC: 031057) has 95.8% identity in 71 AA overlap with SEQ ID NO 17 ---	1-10, 16-23,26
P,X	DATABASE GENESEQ [Online] Accession Number V52136, 23 October 1998 (1998-10-23) BARASH S C ET AL: "Streptococcus pneumoniae genome fragment SEQ ID NO:3" XP002125183 68.5% identity between base 2539-3319 of SEQ ID NO 37 and base 18492-19271 of V52136 Translation has 74.5% identity in 231 AA overlap with SEQ ID NO 40 & WO 98 18931 A (DOUGHERTY BRIAN A ;HUMAN GENOME SCIENCES INC (US); ROSEN CRAIG A) 7 May 1998 (1998-05-07) -----	1,3-7,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00114

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

11-14,16,24,25,27,28,30,31 (completely), 1-10,15,17-23,26,29,32-48 (all partially) i.e. (group of) inventions 1, 3 and 7

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.